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(54) Title: TRICYCLIC NUCLEOSIDE LIBRARY COMPOUNDS, SYNTHESIS, AND USE AS ANTIVIRAL AGENTS

(57) Abstract: Tricyclic nucleoside libraries and library compounds are prepared using combinatorial chemistry and non-combinatorial chemistry methods. Contemplated library compounds are particularly useful in inhibition of viral propagation, and particularly of viral propagation of the HCV virus.

## **TRICYCLIC NUCLEOSIDE LIBRARY COMPOUNDS, SYNTHESIS, AND USE AS ANTIVIRAL AGENTS**

This application claims the benefit of U.S. provisional application number 60/350249, filed January 17, 2002, and U.S. provisional application number 60/395241, filed July 10, 2002, both of which are incorporated by reference herein.

### **Field of The Invention**

The field of the invention is tricyclic nucleoside libraries, compounds of and derived from such libraries, and their use, particularly for treatment of viral infections with HCV, HRV, RSV, HIV, and HBV, as well as treatment of viral infections with viruses of the families Flaviviridae, Paramyxoviridae, Orthomyxoviridae, Picornaviridae, Bunyaviridae, Arenaviridae, and Herpesviridae.

### **Background of The Invention**

Nucleosides and nucleoside analogs frequently interact with many biological targets, and some nucleoside analogues have been used as antimetabolites for treatment of cancers and viral infections. After entry into the cell, many nucleoside analogues can be phosphorylated to monophosphates by nucleoside kinases, and then further phosphorylated by nucleoside monophosphate kinases and nucleoside diphosphate kinases to give nucleoside triphosphates. Once a nucleoside analogue is converted to its triphosphate inside the cell, it can be incorporated into DNA or RNA. Incorporation of certain unnatural nucleoside analogues into nucleic acid replicates or transcripts can interrupt gene expression by early chain termination, or by interfering with function of the modified nucleic acids. In addition, certain nucleoside analogue triphosphates are very potent, competitive inhibitors of DNA or RNA polymerases, which can significantly reduce the rate at which the natural nucleoside can be incorporated. Many anti-HIV nucleoside analogues fall into this category, including 3'-C-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, and 2',3'-didehydro-2',3'-dideoxythymidine.

Various nucleoside analogues can also act in other ways, for example, causing apoptosis of cancer cells and/or modulating immune systems. In addition to nucleoside antimetabolites, a number of nucleoside analogues that show very potent anticancer and antiviral activities act through still other mechanisms. Some well-known nucleoside anticancer drugs are thymidylate synthase inhibitors such as 5-fluorouridine, and adenosine

deaminase inhibitors such as 2-chloroadenosine. A well-studied anticancer compound, neplanocin A, is an inhibitor of S-adenosylhomocysteine hydrolase, which shows potent anticancer and antiviral activities.

Unfortunately, many nucleoside analogues that can inhibit tumor growth or viral  
5 infections are also toxic to normal mammalian cells, primarily because these nucleoside analogues lack adequate selectivity between the normal cells and the virus-infected host cells or cancer cells. For this reason many otherwise promising nucleoside analogues fail to become therapeutics in treatment of various diseases.

Selective inhibition of cancer cells or host cells infected by viruses has been an  
10 important subject for some time, and tremendous efforts have been made to search for more selective nucleoside analogues. In general, however, a large pool of nucleoside analogues is thought to be necessary in order to identify highly selective nucleoside analogues. Unfortunately, the classical method of synthesizing nucleosides and nucleotides having desired physiochemical properties, and then screening them individually, takes a significant  
15 amount of time to identify a lead molecule. Although thousands of nucleoside analogues were synthesized over the past decades, if both sugar and base modifications are considered, many additional analogues are still waiting to be synthesized.

During the last few years, combinatorial chemistry has been used to generate huge numbers of organic compounds other than nucleosides, nucleotides, and their analogs,  
20 resulting in large compound libraries. If nucleosides, nucleotides, and their analogs could be made through a combinatorial chemistry approach, a large number of such compounds could be synthesized within months instead of decades, and large libraries could be developed.

A combinatorial chemistry approach to nucleosides may also encourage a focus beyond previously addressed biological targets. For example, in the past nucleoside  
25 analogues were usually designed as potential inhibitors of DNA or RNA polymerases and several other enzymes and receptors, including inosine monophosphate dehydrogenase, protein kinases, and adenosine receptors. If a vast number of diversified nucleoside analogues could be created, their use may be far beyond these previously recognized biological targets, which would open a new era for the use of nucleoside analogues as human therapeutics.

The generation of combinatorial libraries of chemical compounds other than nucleosides, nucleotides, and their analogs by employing solid phase synthesis is well known in the art. For example, Geysen, et al. (*Proc. Natl. Acad. Sci. USA*, 3998 (1984)) describes the construction of a multi-amino acid peptide library; Houghton, et al. (*Nature*, 354, 84 (1991)) describes the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery; Lam, et al. (*Nature*, 354, 82 (1991)) describes a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin.

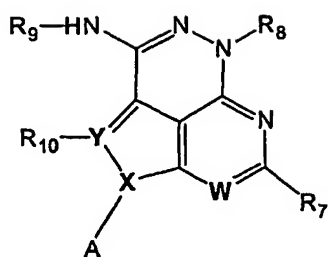
Although a combinatorial chemistry approach has been proven to work well with many types of compounds, there are numerous problems with the generation of nucleoside libraries. Among numerous other difficulties, most nucleoside analogues contain a sugar moiety and a nucleoside base, which are linked together through a glycosidic bond. The formation of the glycosidic bond can be achieved through a few types of condensation reactions. However, most of the reactions do not give a good yield of desired products, which may not be suitable to generation of nucleoside libraries. Moreover, the glycosidic bonds in many nucleosides are labile to acidic condition, and many useful reactions in combinatorial chemistry approaches cannot be used in the generation of nucleoside analogue libraries.

Furthermore, many of the known purine- and pyrimidine-based nucleoside analogs have, despite promising in vitro results, failed to turn into successful drug candidates for human use due to numerous adverse physiological effects. As a result, many researchers focused their attention to areas in pharmaceutical chemistry that appear to present an easier access to potential therapeutic molecules, and there seems to be a lack of methods for generating libraries of nucleosides and nucleotides using solid phase synthesis.

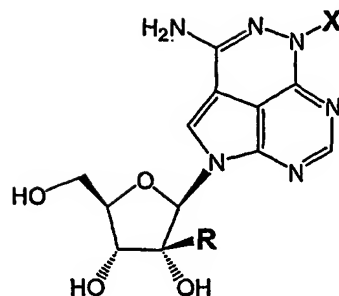
Therefore, there is still a need to provide methods for generation of nucleoside and nucleotide libraries (and especially libraries with unusual heterocyclic bases), as well as compounds from those libraries with desirable therapeutic activity.

### **Summary of the Invention**

The present invention is directed to tricyclic nucleoside libraries and library compounds that are prepared using combinatorial and non-combinatorial chemistry approaches. Generally contemplated compounds will have a structure according to Formula 1, and particularly preferred compounds will have a structure according to Formula 1A (with substituents as defined in the section entitled "Detailed Description").

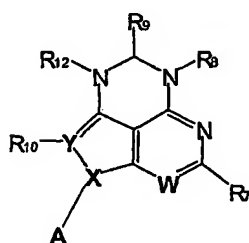


Formula 1

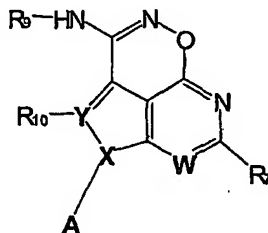


Formula 1A

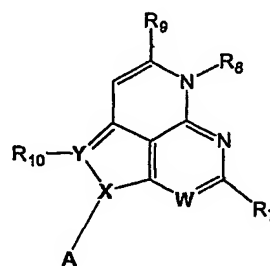
In further contemplated aspects of the inventive subject matter, modifications may be made to at least one of the tricyclic heterocyclic base and the sugar moiety. Consequently, contemplated compounds also include those having a structure according to Formulae 2-7 (with substituents as defined in the section entitled "Detailed Description").



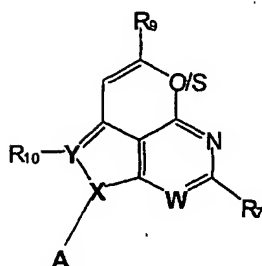
Formula 2



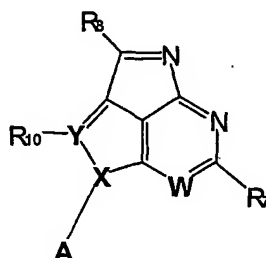
Formula 3



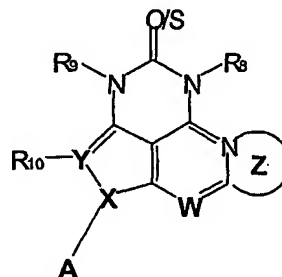
Formula 4



Formula 5



Formula 6



Formula 7

In yet another aspect of the inventive subject matter, contemplated compounds may be used in a method of inhibiting propagation of a virus, wherein the virus is presented with one or more of the contemplated compounds at a concentration effective to reduce the propagation of the virus. Particularly preferred viruses include HCV, HRV, RSV, HIV, HBV,

as well as viruses of the families Flaviviridae, Paramyxoviridae, Orthomyxoviridae, Picornaviridae, Bunyaviridae, Arenaviridae, and Herpesviridae. Consequently, it is contemplated that a pharmaceutical composition may comprise one or more of the compounds according to the inventive subject matter at a concentration effective to reduce  
5 propagation of a virus in a patient infected with the virus.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

### **Detailed Description**

10 The term "nucleoside library" as used herein refers to a plurality of chemically distinct nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs wherein at least some of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs include, or have been synthesized from a common precursor.

For example, a plurality of nucleosides, nucleotides, nucleoside analogs, and/or  
15 nucleotide analogs that were prepared from a protected 1'-chlororibofuranose as a building block/precursor is considered a nucleoside library under the scope of this definition. Therefore, the term "common precursor" may encompass a starting material in a first step in a synthesis as well as a synthesis intermediate (*i.e.*, a compound derived from a starting material). In another example, at least one step in the synthesis of one of the nucleosides,  
20 nucleotides, nucleoside analogs, and/or nucleotide analogs is concurrent with at least one step in the synthesis of another one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and synthesis is preferably at least partially automated. In contrast, a collection of individually synthesized nucleosides, nucleotides, nucleoside analogs, and/or  
nucleotide analogs, and especially a collection of compounds not obtained from a nucleoside  
25 library, is not considered a nucleoside library because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs will not have a common precursor, and because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs are not concurrently produced.

It is further generally contemplated that the complexity of contemplated libraries is at  
30 least 20 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, more typically at least 100 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide

analogs, and most typically at least 1000 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs. Consequently, a typical format of a nucleoside library will include multi-well plates, or a plurality of small volume (*i.e.*, less than 1ml) vessels coupled to each other. The term "library compound" as used herein refers to a nucleoside, nucleotide,  
5 nucleoside analog, and/or nucleotide analog within a nucleoside library.

As also used herein, the terms "heterocycle" and "heterocyclic base" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, wherein the ring includes at least one atom other than a carbon atom. Particularly contemplated heterocyclic bases include 5- and 6-membered rings  
10 with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocycles may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine), and a 6-membered ring fused to  
15 another 6-membered or higher ring (*e.g.*, pyrido[4,5-d]pyrimidine, benzodiazepine). Examples of these and further preferred heterocyclic bases are given below. Still further contemplated heterocyclic bases may be aromatic, or may include one or more double or triple bonds. Still further, contemplated heterocyclic bases may include one or more substituents other than hydrogen, and especially contemplated substituents include those  
20 referenced below. Moreover, suitable heterocyclic bases may further contain at least one hetero atom, such as O, S, N, or P. Contemplated heterocycles or substituted heterocycles are typically attached directly to nucleoside bases or sugars but coupling of the heterocyclic base to the sugar may also include a linker moiety with at least 1-4 atoms between the heterocyclic base and the sugar.

25 As further used herein, the term "sugar" refers to all carbohydrates and derivatives thereof, wherein particularly contemplated derivatives include deletion, substitution or addition of a chemical group in the sugar. For example, especially contemplated deletions include 2'-deoxy and/or 3'-deoxy sugars. Especially contemplated substitutions include replacement of the ring-oxygen with sulfur or methylene, or replacement of a hydroxyl group  
30 with a halogen, an amino, sulfhydryl, or methyl group, and especially contemplated additions include methylene phosphonate groups. Further contemplated sugars also include sugar analogs (*i.e.*, not naturally occurring sugars), and particularly carbocyclic ring systems. The

term "carbocyclic ring system" as used herein refers to any molecule in which a plurality of carbon atoms form a ring, and in especially contemplated carbocyclic ring systems the ring is formed from 3, 4, 5, or 6 carbon atoms. Examples of these and further preferred sugars are given below.

5           The term "nucleoside" refers to all compounds in which a heterocyclic base is covalently coupled to a sugar, and an especially preferred coupling of the nucleoside to the sugar includes a C1'-(glycosidic) bond of a carbon atom in a sugar to a carbon or heteroatom (typically nitrogen) in the heterocyclic base. The term "nucleoside analog" as used herein refers to all nucleosides in which the sugar is not a ribofuranose and/or in which the  
10       heterocyclic base is not a naturally occurring base (e.g., A, G, C, T, I, etc.), however, it also includes naturally occurring nucleosides. It should further be particularly appreciated that the term nucleoside also includes all prodrug forms of a nucleoside, wherein the prodrug form may be activated/converted to the active drug/nucleoside in one or more than one step, and wherein the activation/conversion of the prodrug into the active drug/nucleoside may occur  
15       intracellularly or extracellularly (in a single step or multiple steps). Especially contemplated prodrug forms include those that confer a particular specificity towards a diseased or infected cell or organ, and exemplary contemplated prodrug forms are described in "Prodrugs" by Kenneth B. Sloan (Marcel Dekker; ISBN: 0824786297); "Design of Prodrugs" by Hans Bundgaard (ASIN: 044480675X), or in copending US application number 09/594410, filed  
20       06/16/2000, all of which are incorporated by reference herein.

          Similarly, the term "nucleotide" as used herein refers to a nucleoside that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.). Consequently, the term "nucleotide analog" refers to a  
25       nucleoside analog that is coupled to a 5'-phosphate group (or modified phosphate group, including phosphonate, thiophosphate, phosphate ester, etc.).

          The terms "alkyl" and "unsubstituted alkyl" are used interchangeably herein and refer to any linear, branched, or cyclic hydrocarbon in which all carbon-carbon bonds are single bonds. The term "substituted alkyl" as used herein refers to any alkyl that further comprises a functional group, and particularly contemplated functional groups include nucleophilic (e.g.,  
30       -NH<sub>2</sub>, -OH, -SH, -NC, etc.) and electrophilic groups (e.g., C(O)OR, C(X)OH, etc.), polar groups (e.g., -OH), non-polar groups (e.g., aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., -NH<sub>3</sub><sup>+</sup>), and halogens (e.g., -F, -Cl), and all chemically reasonable combinations



thereof. The terms "alkenyl" and "unsubstituted alkenyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl with at least one carbon-carbon double bond. The term "substituted alkenyl" as used herein refers to any alkenyl that further comprises a functional group, and particularly contemplated functional groups include those discussed  
5 above.

Furthermore, the terms "alkynyl" and "unsubstituted alkynyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl or alkenyl with at least one carbon-carbon triple bond. The term "substituted alkynyl" as used herein refers to any alkynyl that further comprises a functional group, and particularly contemplated  
10 functional groups include those discussed above. The terms "aryl" and "unsubstituted aryl" are used interchangeably herein and refer to any aromatic cyclic alkenyl or alkynyl. The term "substituted aryl" as used herein refers to any aryl that further comprises a functional group, and particularly contemplated functional groups include those discussed above. The term "alkaryl" is employed where the aryl is further covalently bound to an alkyl, alkenyl, or  
15 alkynyl.

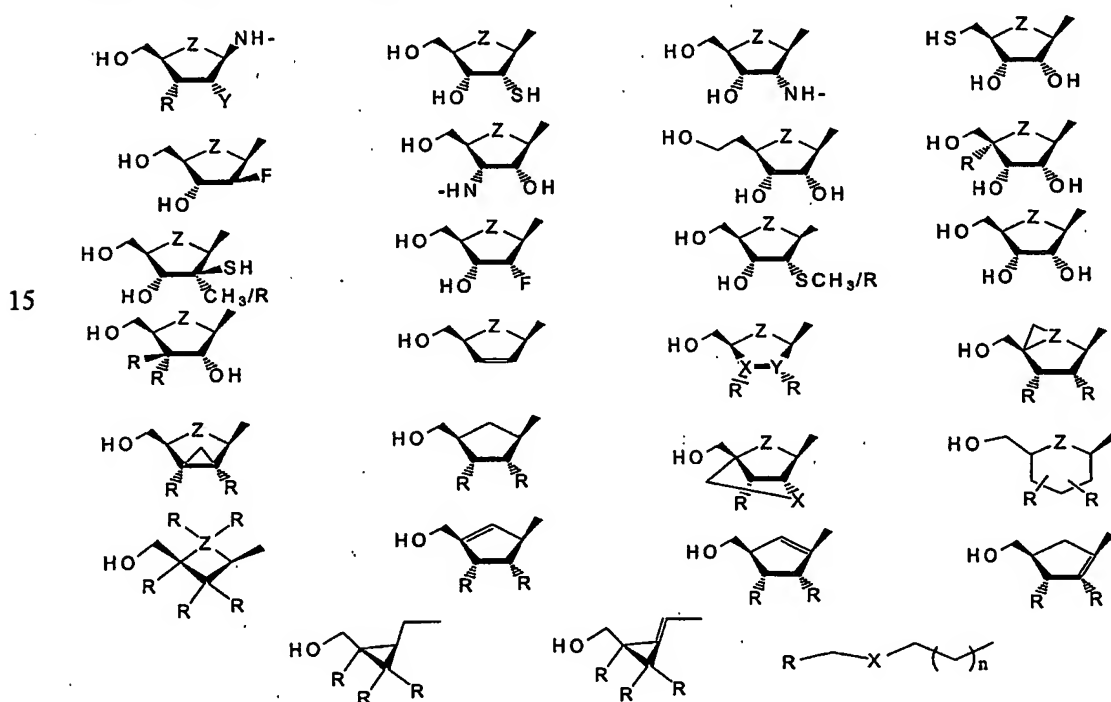
Thus, the term "substituted" as used herein also refers to a replacement of a chemical group or substituent (typically H or OH) with a functional group, and particularly contemplated functional groups include nucleophilic (*e.g.*, -NH<sub>2</sub>, -OH, -SH, -NC, etc.) and electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar  
20 groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, -NH<sub>3</sub><sup>+</sup>), and halogens (*e.g.*, -F, -Cl), and all chemically reasonable combinations thereof.

#### Contemplated Sugars

It is contemplated that suitable sugars will have a general formula of C<sub>n</sub>H<sub>2n</sub>O<sub>n</sub>, wherein n is between 2 and 8, and wherein (where applicable) the sugar is in the D- or L-  
25 configuration. Moreover, it should be appreciated that there are numerous equivalent modifications of such sugars known in the art (sugar analogs), and all of such modifications are specifically included herein. For example, some of the contemplated alternative sugars will include sugars in which the heteroatom in the cyclic portion of the sugar is an atom other than oxygen (*e.g.*, sulfur, carbon, or nitrogen) analogs, while other alternative sugars may not  
30 be cyclic but in a linear (open-chain) form. Suitable sugars may also include one or more double bonds. Still further specifically contemplated alternative sugars include those with one

or more non-hydroxyl substituents, and particularly contemplated substituents include mono-, di-, and triphosphates (preferably as C<sub>5'</sub> esters), alkyl groups, alkoxygroups, halogens, amino groups and amines, sulfur-containing substituents, etc. It is still further contemplated that all contemplated substituents (hydroxyl substituents and non-hydroxyl substituents) may be directed in the alpha or beta position.

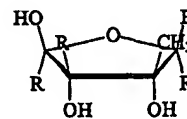
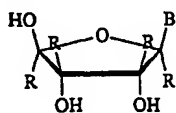
Numerous contemplated sugars and sugar analogs are commercially available. However, where contemplated sugars are not commercially available, it should be recognized that there are various methods known in the art to synthesize such sugars. For example, suitable protocols can be found in "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan (Gordon & Breach Science Pub; ISBN: 3718659212), in U.S. Pat Nos. 4,880,782 and 3,817,982, in WO88/00050, or in EP199,451. An exemplary collection of further contemplated sugars and sugar analogs is depicted below, wherein all of the exemplary sugars may be in D- or L-configuration, and wherein at least one of the substituents (typically H or OH) on the C<sub>1'</sub>-C<sub>5'</sub> atom of the sugar may be in either alpha or beta orientation.



X, Y, Z = O, S, Se, NH, NR, CH<sub>2</sub>, CHR, P(O), P(O)OR  
 R = H, OH, NHR, halo, CH<sub>2</sub>OH, COOH, N<sub>3</sub>, alkyl, aryl, alkynyl, heterocycles, OR, SR, P(O)(OR)<sub>2</sub>  
 OCOR, NHCOR, NHSO<sub>2</sub>R, NH<sub>2</sub>NH<sub>2</sub>, amidine, substituted amidine, guanidine, substituted guanidine

An especially contemplated class of sugars comprises alkylated sugars, wherein one or more alkyl groups are covalently bound to sugar at the C<sub>1'</sub>, C<sub>2'</sub>, C<sub>3'</sub>, C<sub>4'</sub>, or C<sub>5'</sub> atom. In such alkylated sugars, it is especially preferred that the sugar portion comprises a furanose (most

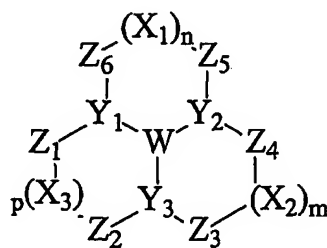
preferably a D- or L-ribofuranose), and that at least one of the alkyl groups is a methyl group. Of course, it should be recognized that the alkyl group may or may not be substituted with one or more substituents. Two exemplary classes of particularly preferred sugars are depicted below:



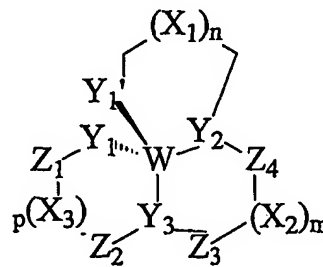
in which B is hydrogen, hydroxyl, or a heterocyclic base, R is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl (branched, linear, or cyclic), with alkyl including between one and twenty carbon atoms.

### Contemplated Heterocyclic Bases

It is generally contemplated that suitable heterocyclic bases include all compounds that comprise at least three cyclic structures (preferably with at least one atom other than a carbon atom), wherein each of the cyclic structures shares at least one atom with another of the at least three cyclic structures. As used herein, the term "cyclic structure" refers to a plurality of atoms that are covalently bound to form a ring. As further used herein, the term "shares at least one atom" means that a particular atom is part of the chain of atoms that form a cyclic structure in at least two cyclic structures. Consequently, contemplated cyclic structures include annulated ring systems, spiro-ring systems, and any reasonable combination thereof. Exemplary heterocyclic bases are depicted below, in which Formula A represents an annulated tricyclic compound, and Formula B represents a spiro-tricyclic compound



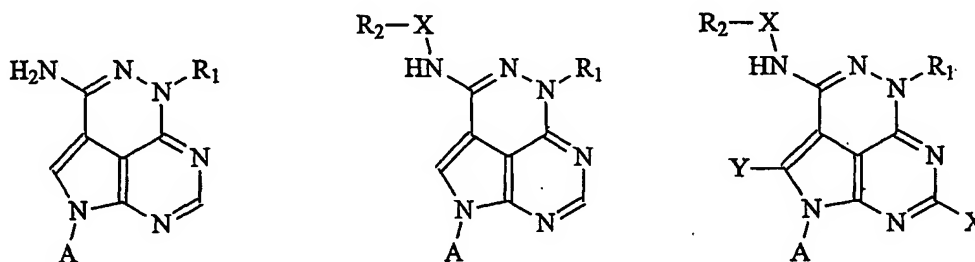
Formula A

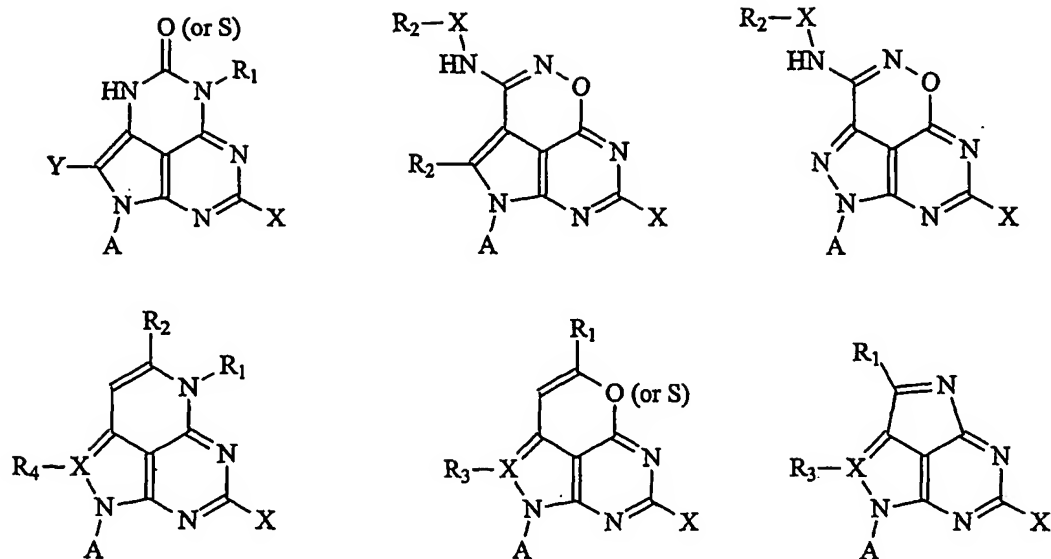


Formula B

wherein n, m, and p are independently selected between 1 and 10; X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are independently selected from CRR', NR, O, and S; Y<sub>1</sub>, Y<sub>1</sub>', Y<sub>2</sub>, and Y<sub>3</sub> are independently selected from CR, or N; Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, Z<sub>4</sub>, Z<sub>5</sub>, and Z<sub>6</sub> are independently selected from CRR', NR, O, and S; W is C or N; and wherein R and R' are independently hydrogen, aryl, alkyl, alkenyl, or alkynyl, which may or may not be further substituted. Still further, where appropriate, R or R' may also represent a covalent bond. Thus, contemplated tricyclic compounds may include one or more double bonds. Consequently, one or more substituents R and/or R' may not be present in the Formulae A and B.

Particularly contemplated cyclic structures include 3-membered, 4-membered, 5-membered, 6-membered, and 7-membered rings, all of which may be partially or entirely desaturated or aromatic. However, it should be recognized that a particular ring size is not limiting to the inventive subject matter. Moreover, while it is generally preferred that contemplated nucleosides comprise a tricyclic heterocyclic base, it should also be appreciated that alternative heterocyclic bases may include additional cyclic structures, which may or may not be annulated or otherwise coupled to the tricyclic heterocyclic base. Still further, it is contemplated that suitable cyclic structures may be formed from various atoms, and especially preferred atoms include carbon, nitrogen, sulfur, selenium, oxygen, and phosphorous. In further contemplated aspects, however, it is also contemplated that appropriate atoms may also include atoms other than carbon, nitrogen, sulfur, selenium, oxygen, and phosphorous, and all atoms are contemplated so long as such atoms may be part of at least one cyclic structure. Still further contemplated exemplary tricyclic heterocyclic base are depicted below.





wherein the substituents A, X, Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are defined as in the respective portions of the detailed description below (*e.g.*, section entitled "Contemplated Libraries and Nucleosides").

### Contemplated Solid Phases

It is generally contemplated that all known types of solid phases are suitable for use herein, so long as contemplated nucleosides (or sugar, or heterocyclic base) can be coupled to such solid phases, and so long as the coupled nucleoside (or sugar, or heterocyclic base) will remain coupled to the solid phase during at least one chemical reaction on the nucleoside (or sugar, or heterocyclic base). Especially contemplated solid phases (*i.e.*, solid supports) include Merrifield resins, ArgoGel (available from Argonaut, San Francisco, CA), Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), TentaGel S AC, TentaGel PHB, or TentaGel S NH<sub>2</sub> resin (polystyrene-polyethylene glycol copolymer resins available from Rappe Polymere, Tubingen, Germany). Alternatively, contemplated solid supports may also include glass, as described in U. S. Pat. No. 5,143,854. Another preferred solid support comprises a "soluble" polymer support, which may be fabricated by copolymerization of polyethylene glycol, polyvinylalcohol, or polyvinylalcohol with polyvinyl pyrrolidone or derivatives thereof (*e.g.*, see Janda and Hyunsoo (1996) *Methods Enzymol.* 267:234-247; Gravert and Janda (1997) *Chemical Reviews* 97:489-509; and Janda and Hyunsoo, PCT publication No. WO 96/03418).

Consequently, it should be recognized that there are numerous methods of coupling nucleosides, sugars, or heterocyclic bases to solid phases that may be appropriate, and a particular method will generally depend on the particular type of solid phase and/or type of sugar. Thus, all of such known methods are contemplated suitable for use herein, and  
5 exemplary suitable solid phase coupling reactions are described, for example, in "Organic Synthesis on Solid Phase Supports, Linkers, Reactions" by Florencio Zaragoza Dorwald et al. John Wiley & Sons; ISBN: 3527299505, or in "Solid-Phase Synthesis and Combinatorial Technologies" by Pierfausto Seneci, John Wiley & Sons; ISBN: 0471331953.

#### **Contemplated Combinatorial Reactions**

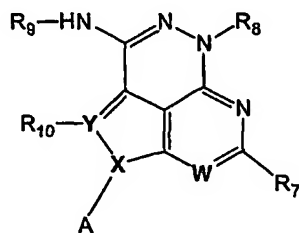
10 It is generally contemplated that all known types of combinatorial reactions and/or reaction sequences may be used in conjunction with the teaching presented herein so long as such combinatorial reactions between a substrate and at least two distinct reagents will result in at least two distinct products. Contemplated combinatorial reactions and/or reaction sequences may therefore be performed sequentially, in parallel, or in any chemically  
15 reasonable combination thereof. It is still further contemplated that suitable combinatorial reactions and/or reaction sequences may be performed in a single compartment or multiple compartments. Preferred combinatorial reactions and/or reaction sequences include at least one step in which a substrate or reaction intermediate is coupled to a solid phase (which may include the wall of the reaction compartment or a solid or soluble polymers), and that the  
20 solid phase is physically separated from another substrate on another solid phase. While not limiting to the inventive subject matter, it is generally preferred that contemplated solid phase synthesis is at least partially automated. There are numerous methods and protocols for combinatorial chemistry known in the art, and exemplary suitable protocols and methods are described in "Solid-Phase Synthesis and Combinatorial Technologies" by Pierfausto Seneci  
25 (John Wiley & Sons; ISBN: 0471331953) or in "Combinatorial Chemistry and Molecular Diversity in Drug Discovery" by Eric M. Gordon and James F. Kerwin (Wiley-Liss; ISBN: 0471155187).

While it is generally preferred that contemplated compounds are synthesized using a library approach, it should be recognized that all of the contemplated compounds may also be  
30 synthesized individually in a classical single or multi-step reaction. For example, a heterocyclic base may be prepared separately from a sugar, and the heterocyclic compound may then be covalently coupled to the sugar in a subsequent reaction.

**Contemplated Libraries and Nucleosides**

The present invention is generally directed to tricyclic nucleoside libraries and library compounds within these libraries, each of which may be synthesized by medicinal and/or combinatorial approaches using solution- and/or solid-phase strategies.

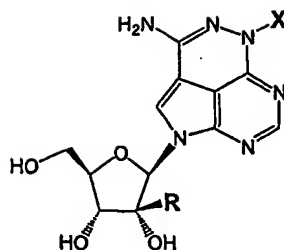
- 5 In one aspect of the inventive subject matter, tricyclic nucleoside libraries will comprise library compounds according to **Formula 1** below



*Formula 1*

- wherein A is a sugar as defined above, as contemplated above in the section entitled
- 10 "Contemplated Sugars", or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>8</sub> is H, C<sub>1</sub>-C<sub>8</sub>-alkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>8</sub>-alkenyl, C<sub>1</sub>-C<sub>8</sub>-alkynyl (all of which may be linear, branched, or cyclic), C<sub>3</sub>-C<sub>15</sub>-aryl, alkaryl, C<sub>3</sub>-C<sub>15</sub>-heterocycle; R<sub>9</sub> is H, OH, SH, CN, SR, OR,
- 15 SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen,
- 20 CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

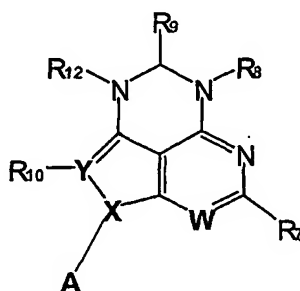
Especially preferred compounds of this type will have a general structure according to **Formula 1A** below:



Formula 1A

wherein R is hydrogen or a lower alkyl, and most preferably methyl, and wherein X is hydrogen, alkyl (and especially lower alkyl), or alkaryl. Particularly preferred lower alkyls include methyl, ethyl, and hydroxyalkyl, and especially preferred alkaryls include CH<sub>2</sub>-Phenyl.

In another aspect of the inventive subject matter, contemplated tricyclic libraries will comprise library compounds according to Formula 2 below



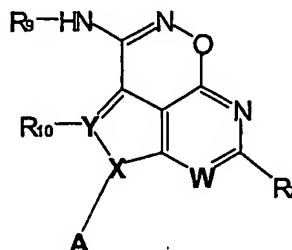
Formula 2

wherein A is a sugar as defined above, as contemplated above in the section entitled "Contemplated Sugars", or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>8</sub>, R<sub>9</sub>, R<sub>12</sub> are independently H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or



C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

In yet another aspect of the inventive subject matter, tricyclic libraries will comprise library compounds according to **Formula 3** below



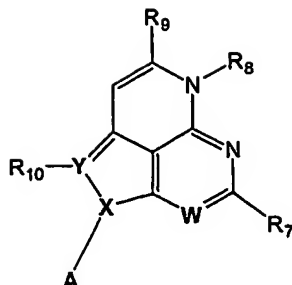
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*Formula 3*

wherein A is a sugar as defined above, as contemplated above in the section entitled "Contemplated Sugars", or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

In a still further aspect of the inventive subject matter, substituted tricyclic libraries will comprise library compounds according to **Formula 4** below:

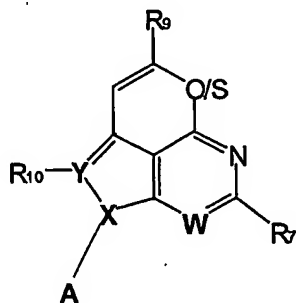
20



Formula 4

wherein A is a sugar as defined above, as contemplated above in the section entitled “Contemplated Sugars”, or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>8</sub> and R<sub>9</sub> are independently H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

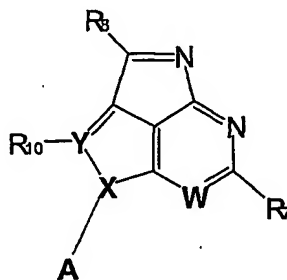
In another aspect of the inventive subject matter, substituted tricyclic libraries will comprise library compounds according to Formula 5 below:



Formula 5

wherein A is a sugar as defined above, as contemplated above in the section entitled "Contemplated Sugars", or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

In a further aspect of the inventive subject matter, substituted tricyclic libraries will comprise library compounds according to Formula 6 below:

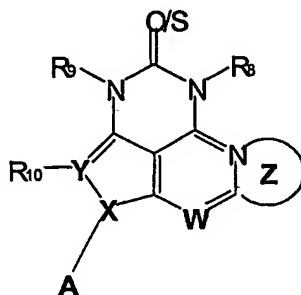


Formula 6

wherein A is a sugar as defined above, as contemplated above in the section entitled "Contemplated Sugars", or as described below at Formula 8. R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH. R<sub>8</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub>

alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings.

In yet a further aspect of the inventive subject matter, substituted tricyclic libraries will comprise library compounds according to **Formula 7** below



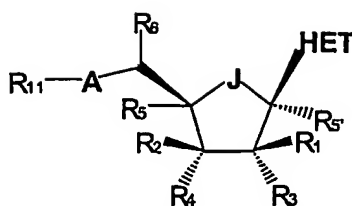
*Formula 7*

wherein A is a sugar as defined above, as contemplated above in the section entitled "Contemplated Sugars", or as described below at Formula 8. R<sub>8</sub> and R<sub>9</sub> are independently H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R. R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; X, Y, W are independently N, C, CH, CR, S, or P; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings; and wherein



is an aromatic ring or a heterocyclic ring fused to the tricyclic compound, each of which may further be substituted.

In all of the above depicted compounds (Formulae 1-7), it is generally contemplated that A represents a sugar, and all contemplated sugars are deemed suitable for use herein. However, in a particularly contemplated aspect of the inventive subject matter, the sugar A has a structure according to Formula 8:



Formula 8

in which HET represents any one of the contemplated tricyclic heterocyclic bases (which may also be in alpha orientation (not shown)); R<sub>1</sub> and R<sub>2</sub> are independently H, OH, CH<sub>3</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, CCl<sub>3</sub>, CHCl<sub>2</sub>, CH<sub>2</sub>Cl, CH<sub>2</sub>OH, CN, CH<sub>2</sub>CN, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NHR, CH<sub>2</sub>OR, CHO, CH<sub>2</sub>COR, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring, halogen (*i.e.*, F, Cl, Br, or I), N<sub>3</sub>, NH<sub>2</sub>, NRR'; R<sub>3</sub> and R<sub>4</sub> are independently H, OH, SH, NH<sub>2</sub>, NHR, OR, SR, CH<sub>2</sub>OH, COOH, halogen, P(O)(OR)<sub>2</sub>. Moreover, where one of R<sub>2</sub> and R<sub>4</sub>, and one of R<sub>1</sub> and R<sub>3</sub> are null, the chemical bond between the C<sub>2</sub>' and C<sub>3</sub>' atom in the sugar is a double bond. R<sub>5</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently H, NH<sub>2</sub>, hydrazino, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings; R<sub>11</sub> is H, RC(O)-, H<sub>2</sub>NCH(R)-CO, phosphonate, triphosphate, diphosphate, monophosphate, or a 3',5'-cyclic phosphate and/or phosphonate; A may be a covalent bond between R<sub>11</sub> and the C<sub>5</sub>'-atom, O, CH<sub>2</sub>, CF<sub>2</sub>, CCl<sub>2</sub>, S, NH, NR; and J may be O, S, NH, NR, CH<sub>2</sub>, CH=CHR, or CHR; wherein R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, or C<sub>2</sub>-C<sub>8</sub> alkynyl (all of which may be linear, branched, or cyclic), C<sub>5</sub>-C<sub>12</sub> heterocycles or C<sub>5</sub>-C<sub>12</sub> aromatic rings. It should still further be recognized that while suitable sugars will typically be in D-configuration, sugars in L-configuration are also specifically contemplated.

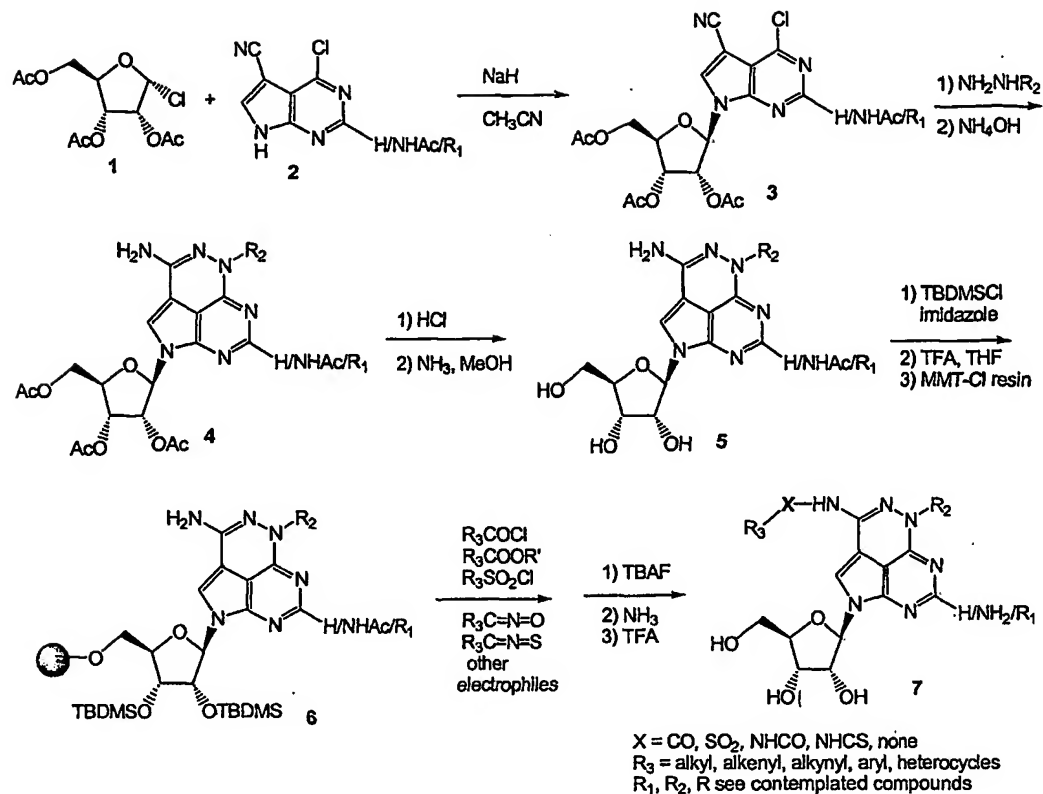
### Synthesis of Contemplated Libraries and Compounds

It is generally contemplated that all libraries and library compounds may be synthesized in a combinatorial approach and/or classic synthetic approach from various starting materials. For example, while in some cases synthesis will begin from a modified heterocyclic base that is subsequently coupled to a sugar, other synthetic routes may include those in which a nucleoside is modified to yield the tricyclic fused nucleosides. However, in especially preferred aspects, the tricyclic heterocyclic base is typically formed from an appropriately substituted 6,7-disubstituted heterocyclic base (which may or may not be a

purine-type heterocyclic base). Many of such 6,7-disubstituted heterocyclic bases are commercially available or may be made from commercially available precursors using protocols well known in the art.

*Synthesis of Exemplary Libraries and Library Compounds*

5           In one aspect of the inventive subject matter, a tricyclic nucleoside library with library compounds according to Formula 1 (*supra*) may be prepared following an exemplary synthetic route as depicted in Scheme 1 below. Here, a 7-deaza-6,7-disubstituted purine heterocyclic base is coupled to an appropriately protected (and activated) sugar to yield the corresponding nucleoside. The so formed nucleoside is then reacted with substituted  
10   hydrazine (or a plurality of chemically distinct substituted hydrazines) and aqueous ammonia to form the third ring. Where chemically distinct substituted hydrazines are employed, the products will be substituted in the third ring with distinct substituents. Thus, a first set of chemically distinct molecules may be prepared. In still further reactions as depicted below, the so prepared tricyclic nucleosides may then be coupled to a solid phase and further  
15   modified at one or more positions in the heterocyclic base and/or sugar. For example, the amino group in the third ring may be used as a nucleophilic group for a reaction to further diversify with a plurality of electrophilic (or otherwise reactive) reagents.



Scheme 1

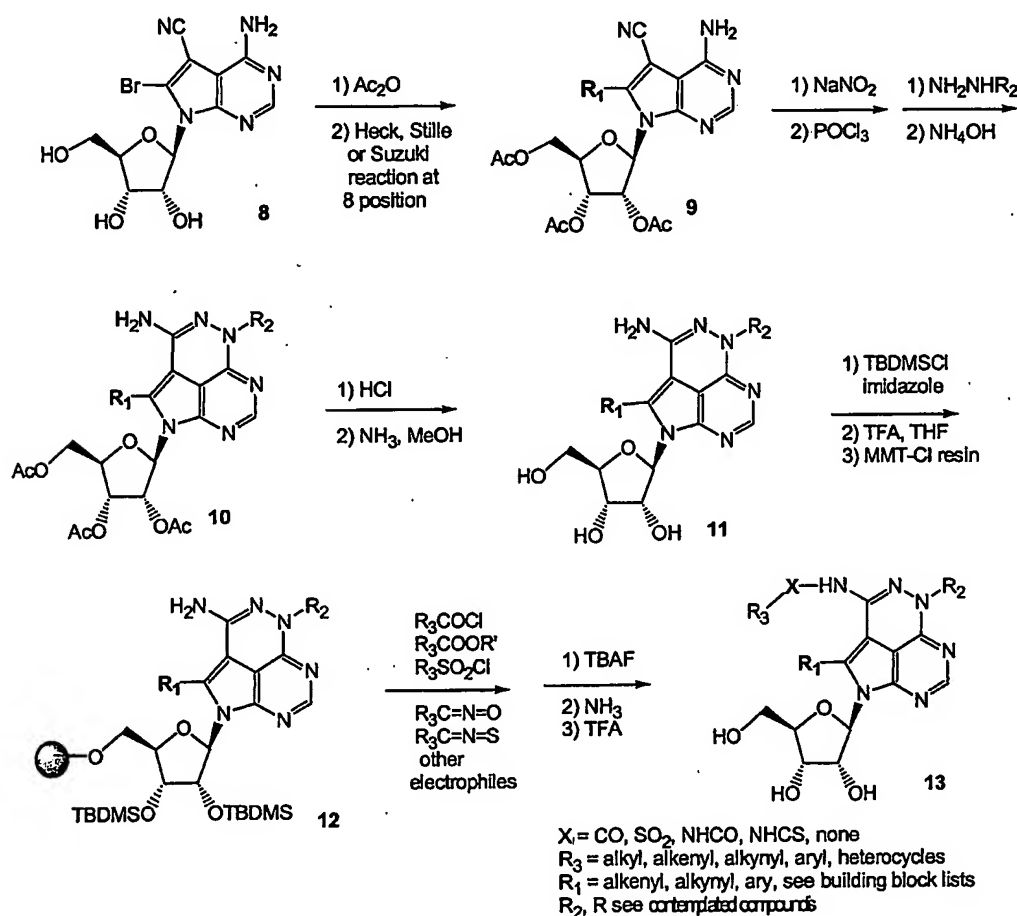
### Exemplary Modifications on the Tricyclic Heterocyclic Base

- In yet further contemplated aspects of the inventive subject matter, alternative and/or additional modifications may be introduced in the tricyclic heterocyclic base. For example, where desirable, a substituent may be added to the 8-position (numbering relative to the purine skeleton) by starting from an appropriately substituted and protected 8-Br-purine nucleoside. Of course, it should be recognized that the 8-Br-purine nucleoside need not be limited to a purine base, but that the purine base may be modified (*e.g.*, deaza purine).
- Scheme 2** depicts an exemplary synthetic route in which the 8-bromo group of a 7-deaza-6,7-disubstituted purine nucleoside is replaced with a desired nucleophile (preferably in a C-C-bond formation, *e.g.*, via Heck, Stille, or Suzuki reaction) to yield the corresponding 8-substituted-7-deaza-6,7-disubstituted purine nucleoside.

- The so formed 8-substituted nucleoside may then be reacted with substituted hydrazine (or a plurality of chemically distinct substituted hydrazines) and aqueous ammonia to form the third ring as already exemplified in Scheme 1 above. Thus, where chemically

distinct substituted hydrazines are employed, the products will be substituted in the third ring with distinct substituents. Consequently, a first set of chemically distinct molecules may be prepared. In still further reactions as depicted below, the so prepared tricyclic nucleosides may then be coupled to a solid phase and further modified at one or more positions in the

5 heterocyclic base and/or sugar. For example, the amino group in the third ring may be used as a nucleophilic group for a reaction to further diversify with a plurality of electrophilic (or otherwise reactive) reagents.



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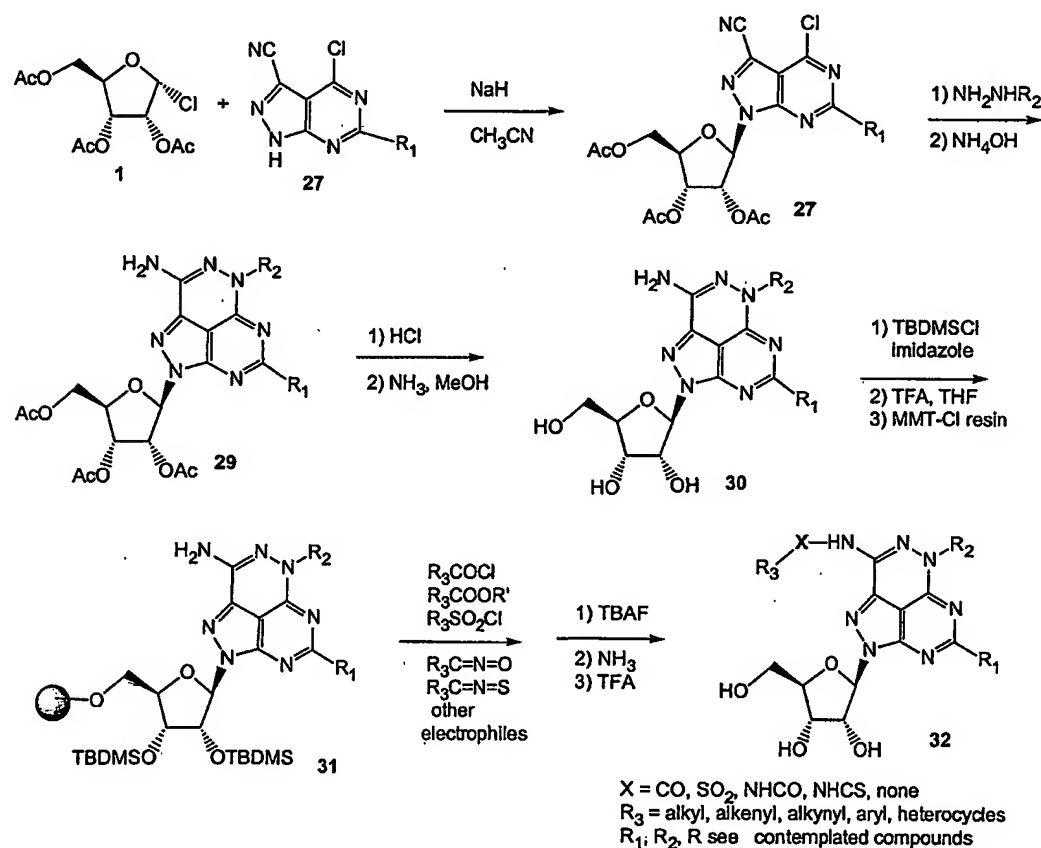
Scheme 2

In yet another aspect of the inventive subject matter, tricyclic nucleoside libraries may be prepared in which the heterocyclic base (as calculated from the purine skeleton) comprises an additional nitrogen atom in the 8-position. Here, as depicted in Scheme 3 below, a 7-deaza-8-aza-2,6,7-trisubstituted purine is coupled to an appropriately protected (and

15 activated) sugar. The so formed nucleoside is then subjected to one or more reactions



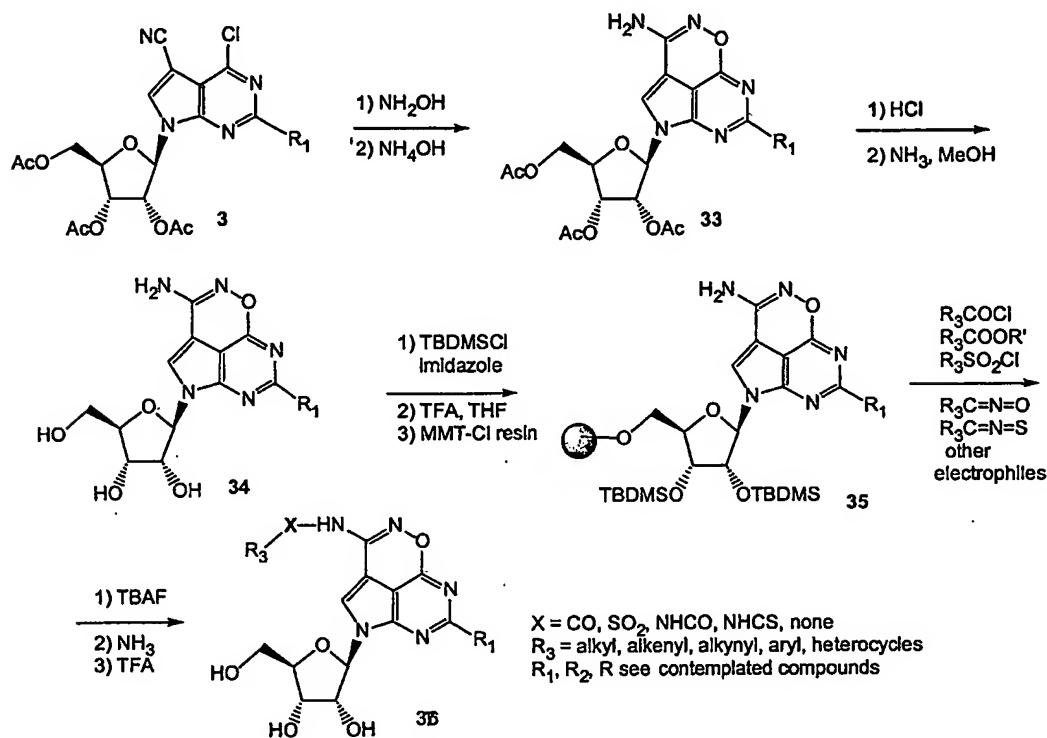
involving the 6- and 7-substituent to form the third ring in a manner substantially the same as described for Schemes 1 and 2 above. Diversity may again be imparted by reacting the substituted nucleosides with a plurality of chemically distinct substituted hydrazines to form the third ring. Furthermore, as also depicted in Schemes 1 and 2 above, additional diversity may be created by coupling the so prepared tricyclic nucleosides to a solid phase and modification of the tricyclic nucleosides at one or more positions in the heterocyclic base and/or sugar. For example, the amino group in the third ring may be used as a nucleophilic group for a reaction to further diversify with a plurality of electrophilic (or otherwise reactive) reagents.



Scheme 3

In still further aspects of modifications of the tricyclic heterocyclic base, a nitrogen atom may be replaced with an oxygen atom as depicted in Scheme 4 below. In this exemplary synthetic route, a 6-7-disubstituted heterocyclic base may be reacted with

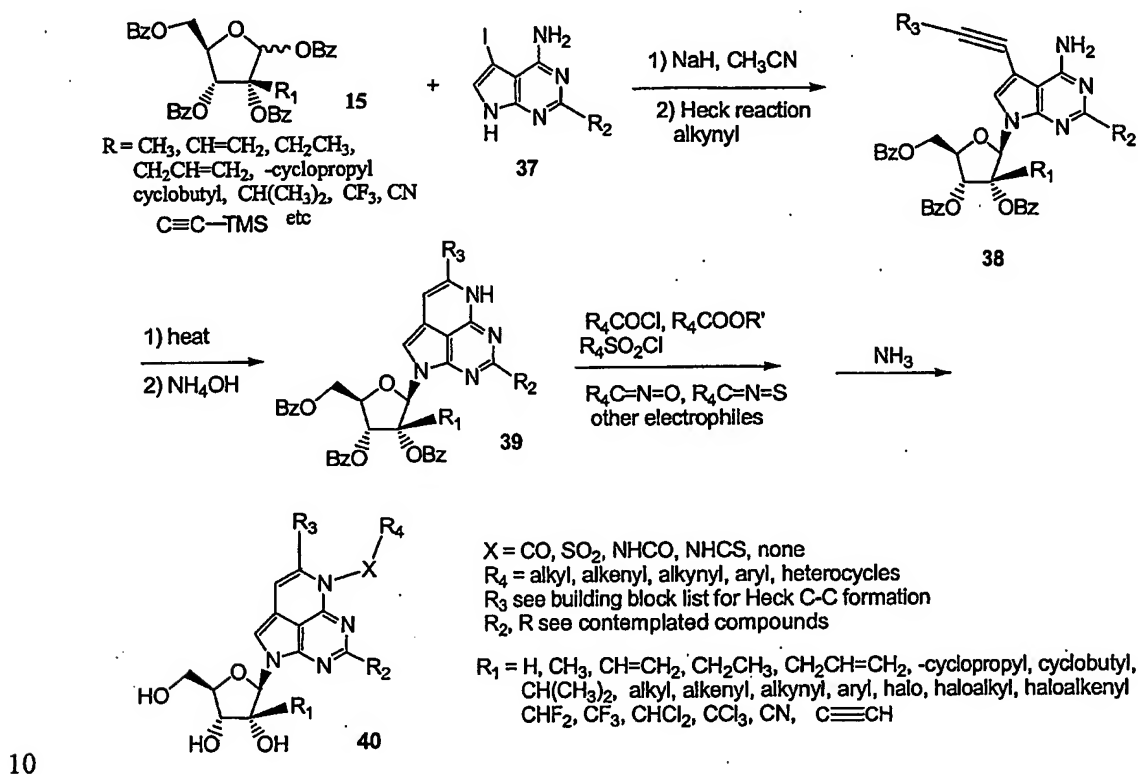
hydroxylamine and aqueous ammonia to form the third ring, which now includes an oxygen atom. Again, and similar to the route already depicted in Scheme 1 above, the so formed tricyclic nucleoside may then be coupled to a solid phase and further modified at one or more positions in the heterocyclic base and/or sugar. For example, the amino group in the third ring may be used as a nucleophilic group for a reaction to further diversify with a plurality of electrophilic (or otherwise reactive) reagents.



Scheme 4

Alternatively, a nitrogen atom in the tricyclic base may also be replaced with a carbon atom as depicted in the exemplary synthetic route of Scheme 5 below. Here, a C2'-substituted and suitable protected sugar is reacted with a 7-deaza-2,6,7-trisubstituted purine heterocyclic base to form the corresponding nucleoside to form the corresponding 7-deaza-2,6,7-trisubstituted purine nucleoside. The iodine in the 7-position is then replaced with a substituted alkynyl in a C-C forming reaction (e.g., in a Heck, Stille, or Suzuki reaction). Where a plurality of chemically distinct substituted alkynyls is employed, diversity may be generated.

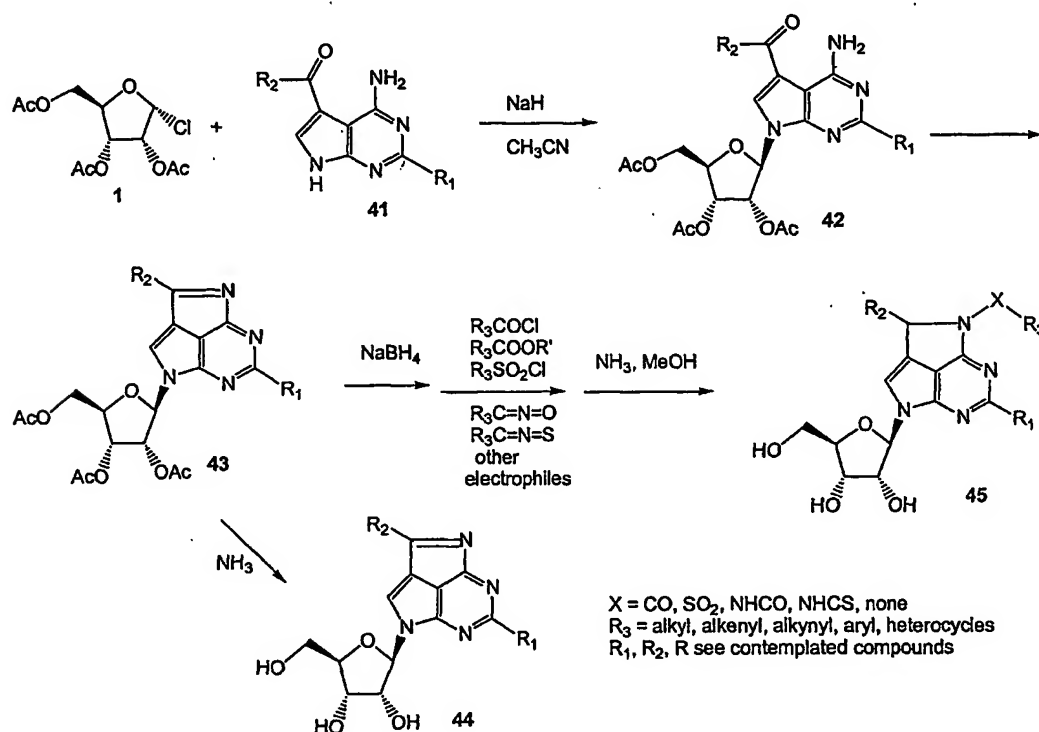
Heating in the presence of aqueous ammonia will lead to the formation of the third ring to yield the tricyclic heterocyclic nucleoside (the third ring is formed in a reaction involving the triple bond of the 7-substituent and the nucleophilic substituent of the 6-position; consequently, the atoms distal to the former triple bond will form the substituent that is vicinal to the nitrogen heteroatom in the third ring). In still further reaction steps, the so formed tricyclic heterocyclic nucleoside may be derivatized at the nitrogen atom in the third ring by replacing the hydrogen atom with an electrophile (or otherwise reactive compound). Deprotection of the sugar OH protecting groups will then yield the corresponding substituted tricyclic nucleosides.



Scheme 5

In yet further contemplated modifications of the tricyclic heterocyclic base, the third ring may be also formed by five atoms (with at least one heteroatom) as depicted in Scheme 6 below. Here, a 7-deaza-6,7-disubstituted purine is coupled to an appropriately protected (and activated) sugar following a procedure similar to those shown in Schemes 1-3 above. The 6-substituent of the 7-deaza-6,7-disubstituted purine includes a nucleophilic group, while the 7-substituent includes an electrophilic center.

Upon proper reaction conditions (*e.g.*, thermal activation), the third ring is formed in a reaction involving the electrophilic center of the 7-substituent and the nucleophilic group of the 6-position. Consequently, the atoms distal to the former electrophilic center will form the substituent that is vicinal to the nitrogen heteroatom in the third ring. The so formed protected tricyclic nucleoside may then be deprotected (*e.g.* using ammonia), or further be modified by reacting the nitrogen atom in the third ring via reduction (*e.g.*, using NaBH<sub>4</sub>) with an electrophile or plurality of electrophiles to generate greater diversity.



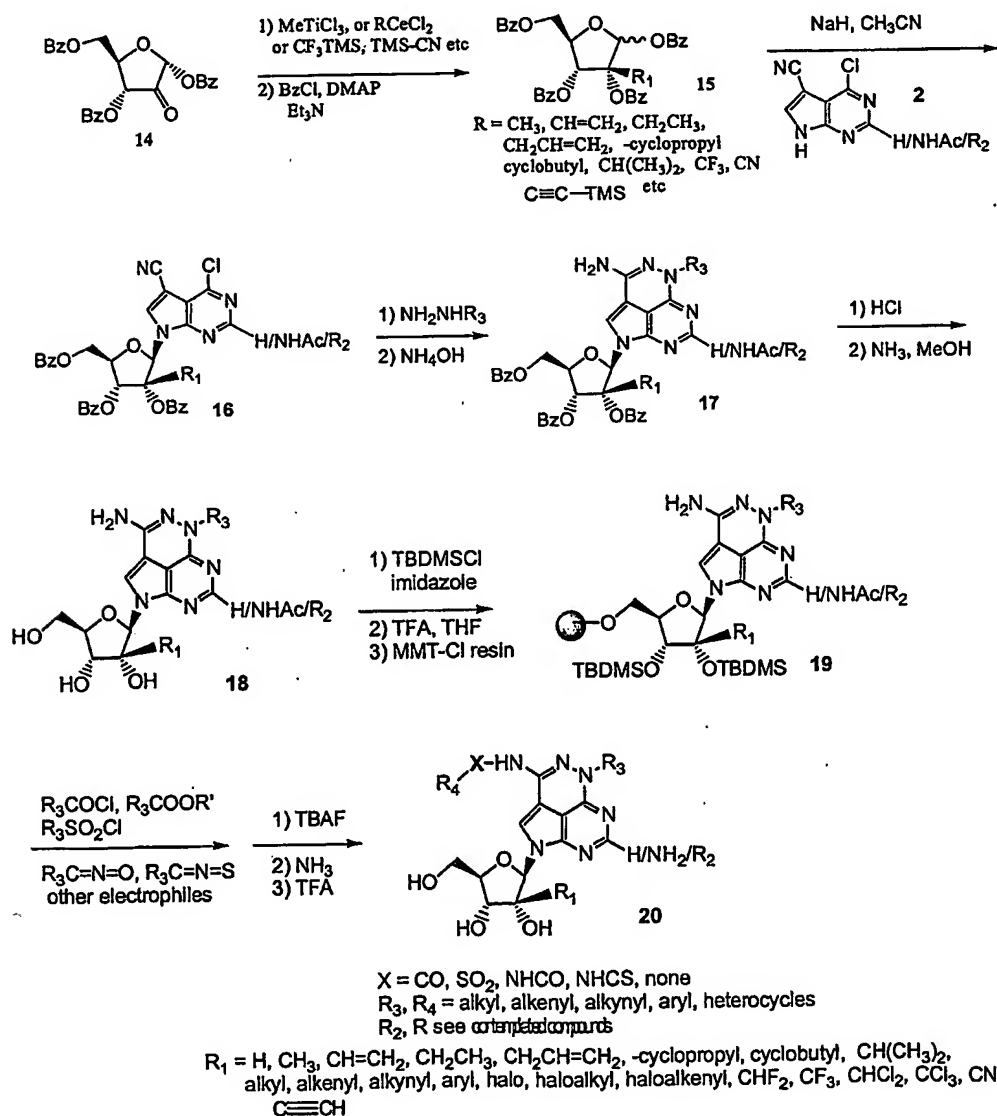
Scheme 6

Similarly, tricyclic heterocyclic nucleosides may be prepared in which the third ring is trisubstituted as depicted in Formulae 2 or 7 (*supra*), or in which the third ring has a single non-nitrogen heteroatom as shown in Formula 5 (*supra*).

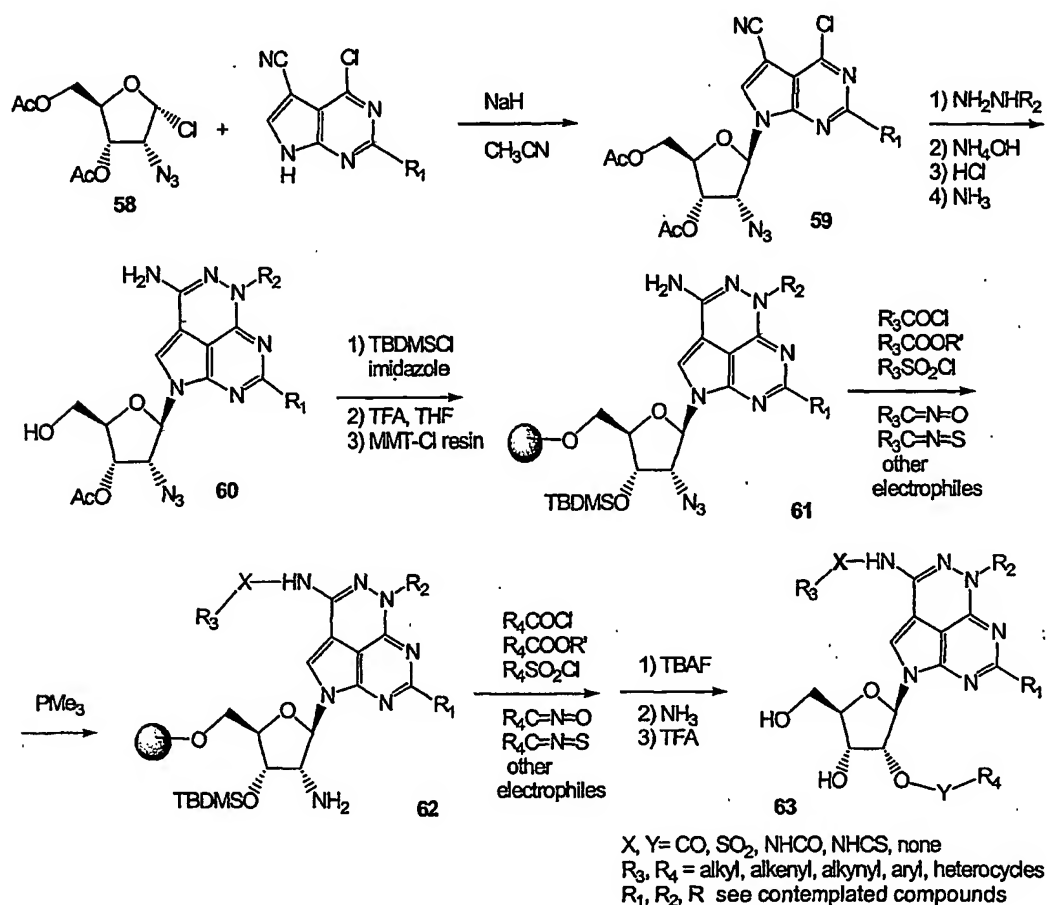
#### Exemplary Modifications on the C2'-position of the Sugar Portion

Where tricyclic nucleosides with a modified sugar portion (*e.g.*, C<sub>2</sub>'-alkyl) are especially desired, contemplated tricyclic nucleoside libraries may be synthesized as shown in Scheme 7 below, in which a suitably protected 2-oxo-sugar is reacted with an

- appropriately activated alkyl (or alkenyl, alkynyl, etc.) substrate to form the corresponding protected C<sub>2</sub>'-substituted sugar. The so prepared C<sub>2</sub>'-substituted sugar is then coupled to a 7-deaza-6,7-disubstituted purine heterocyclic base to yield the corresponding C<sub>2</sub>'-substituted-7-deaza-6,7-disubstituted purine nucleoside, which is then further reacted to the tricyclic nucleoside in a procedure substantially identical to those shown in Schemes 1 and 2 above. In still further reactions, the tricyclic nucleoside may then be coupled to a solid phase, and further be modified at one or more positions in the heterocyclic base and/or sugar following a protocol substantially identical to that shown in Schemes 1 and 2 above.



Alternatively, as depicted in Scheme 8 below, a tricyclic nucleoside library may be prepared by coupling a 7-deaza-2,6,7-trisubstituted purine heterocyclic base to a C<sub>2</sub>'-azido sugar (which may or may not be appropriately protected and activated) following a procedure essentially as that described in Scheme 1. The N<sub>3</sub> group in the sugar of the so formed tricyclic nucleosides is then reduced to the corresponding amino group, which may then serve as a nucleophilic group for a reaction with a yet further electrophilic reagent (or plurality of electrophilic reagents where additional diversity is desired).



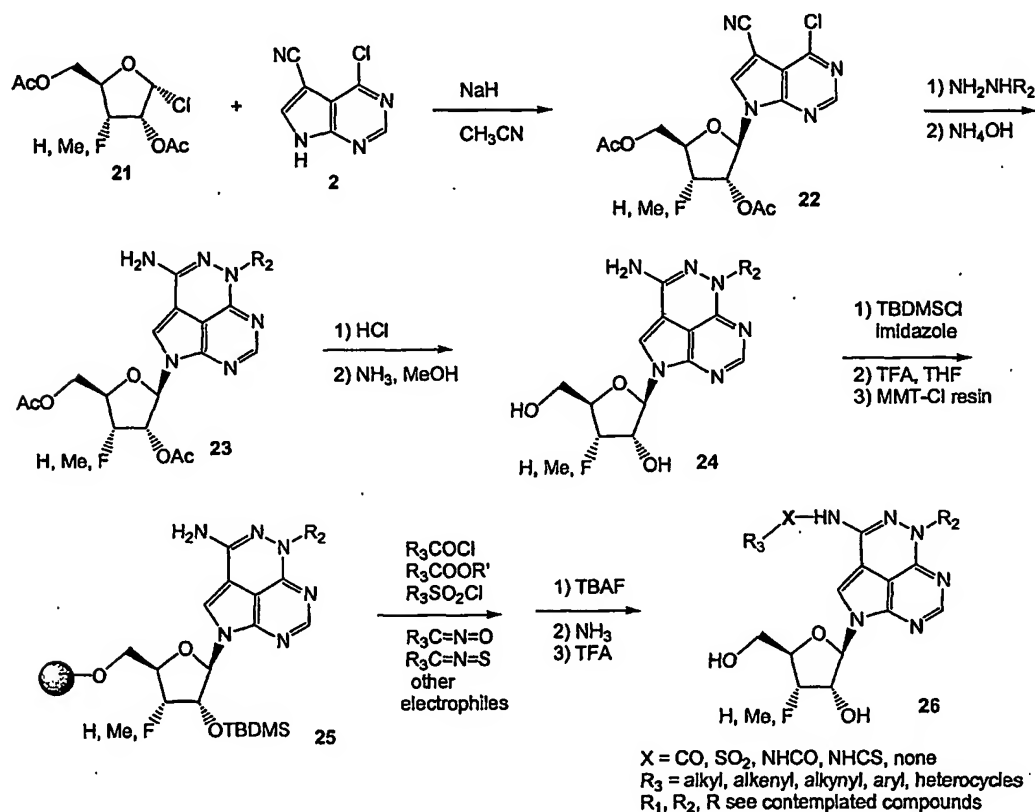
10

Scheme 8

#### Exemplary Modifications on the C3'-position of the Sugar Portion

Where tricyclic nucleosides with a modified sugar portion (e.g., C<sub>3</sub>'-alkyl) are especially desired, contemplated tricyclic nucleoside libraries may be synthesized as shown in Scheme 9 below. Here, an exemplary synthesis starts with coupling of a C<sub>3</sub>'-modified and

suitably protected C<sub>1</sub>'-alpha-chloro sugar to a 7-deaza-6,7-disubstituted purine to form the corresponding 7-deaza-6,7-disubstituted nucleoside. The third ring is formed by reaction of the 7-deaza-6,7-disubstituted nucleoside with a substituted hydrazine, and the so formed tricyclic nucleoside may then be further derivatized at the amino group of the third ring by employing the amino group as a nucleophile for reaction with an electrophilic reagent (or plurality of chemically distinct electrophilic reagents). It should be recognized that the synthetic procedure for the compounds of Scheme 9 will essentially follow the protocol as shown in Scheme 3 above.

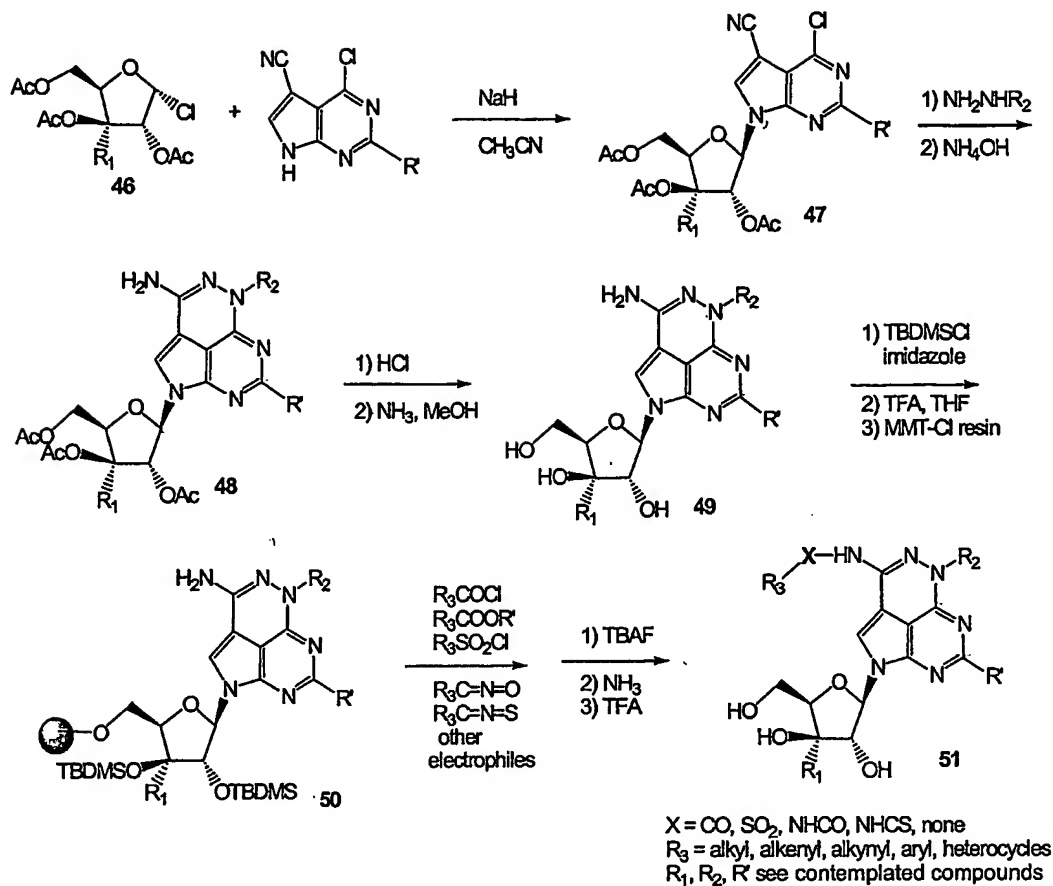


10

Scheme 9

Alternatively, the ribofuranose sugar of Scheme 9 (*supra*) may be replaced with a C3'-substituted sugar (in which the C3'-OH group is in beta orientation) as shown in Scheme 10 below. With respect to the synthetic protocol, the same considerations as for Scheme 1

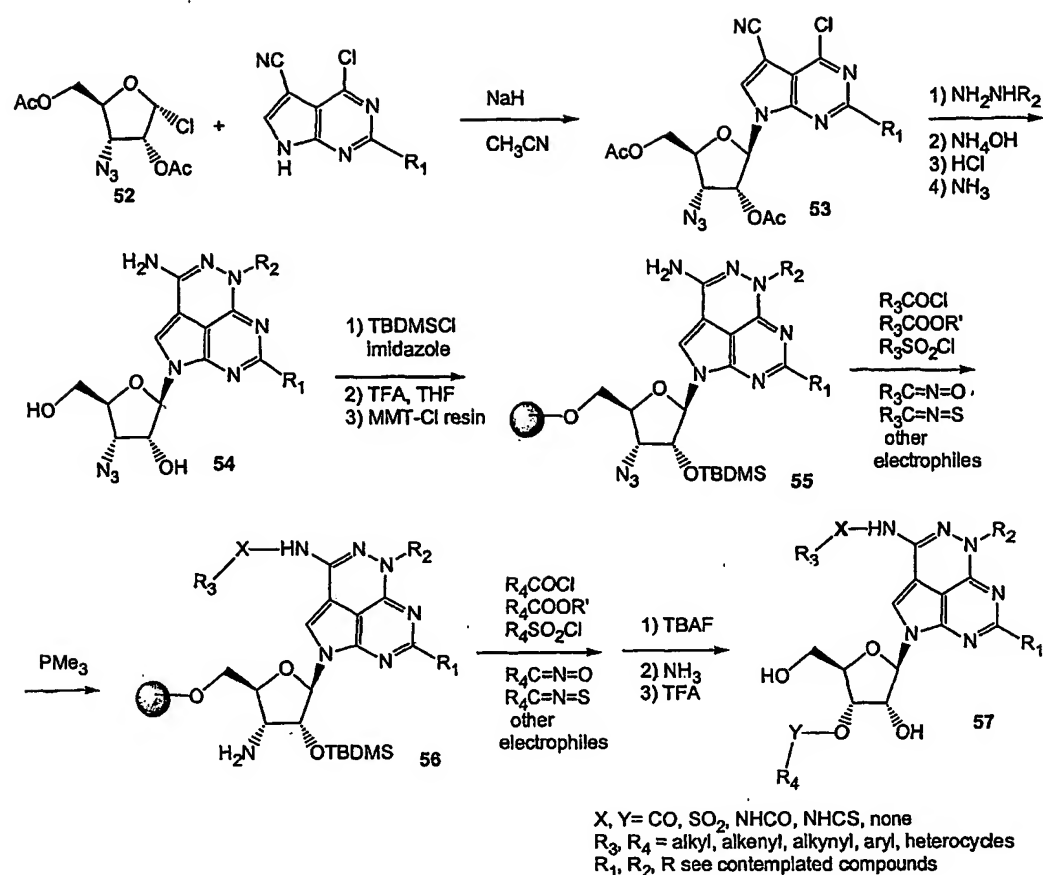
15 (*supra*) apply.



Scheme 10

In a still further exemplary route of preparing C3'-sugar modified tricyclic nucleosides, synthesis may start from a C3'-azido sugar that is coupled to a suitable substituted heterocyclic base. After formation of the third ring (and further optional derivatization of the amino group in the third ring), the azido group is reduced to an amino group that is then employed as a nucleophilic reagent to react with various electrophilic reagents. With respect to the synthetic protocol of **Scheme 11** below, the same considerations as for **Scheme 8** (*supra*) apply.



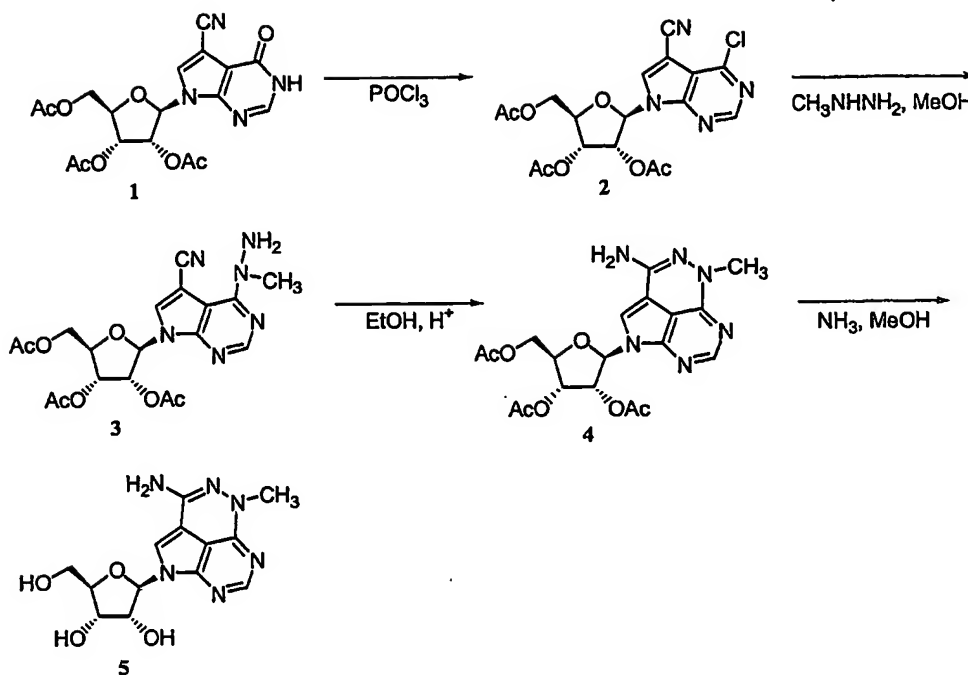


Scheme 11

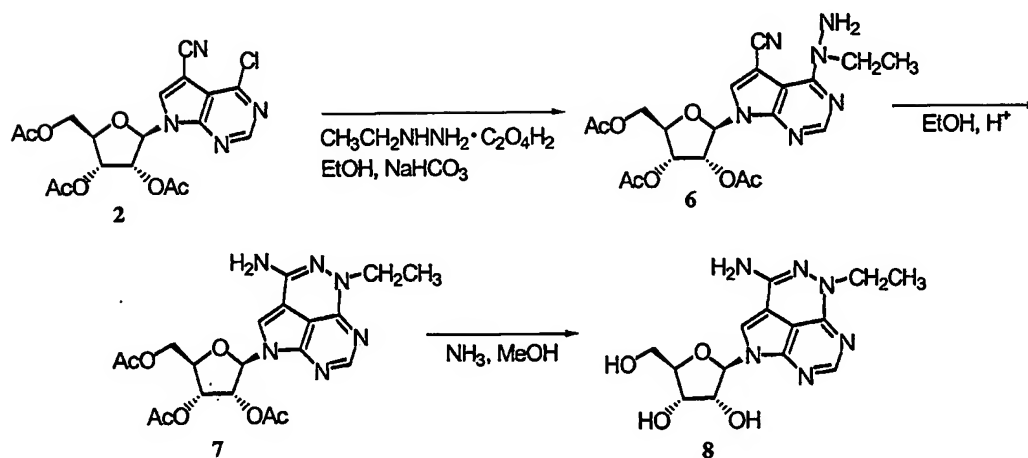
*Synthesis of individual exemplary compounds*

While all or almost all of the compounds may be synthesized in a combinatorial synthetic approach, it should also be appreciated that contemplated compounds may also be obtained in a non-combinatorial approach as depicted in the Schemes 12-17 below.

In one exemplary synthetic route, as depicted in Schemes 12 and 13 below, a tricyclic nucleoside is prepared from a protected 4-chloro-5-cyano-ribofuranosylpyrrolo[2,3-d]pyrimidine that is reacted with methylhydrazine (Scheme 12) or ethylhydrazine (Scheme 13) and ethanol to form the corresponding tricyclic heterocyclic bases. The sugar portions are then deprotected to yield the corresponding nucleosides.

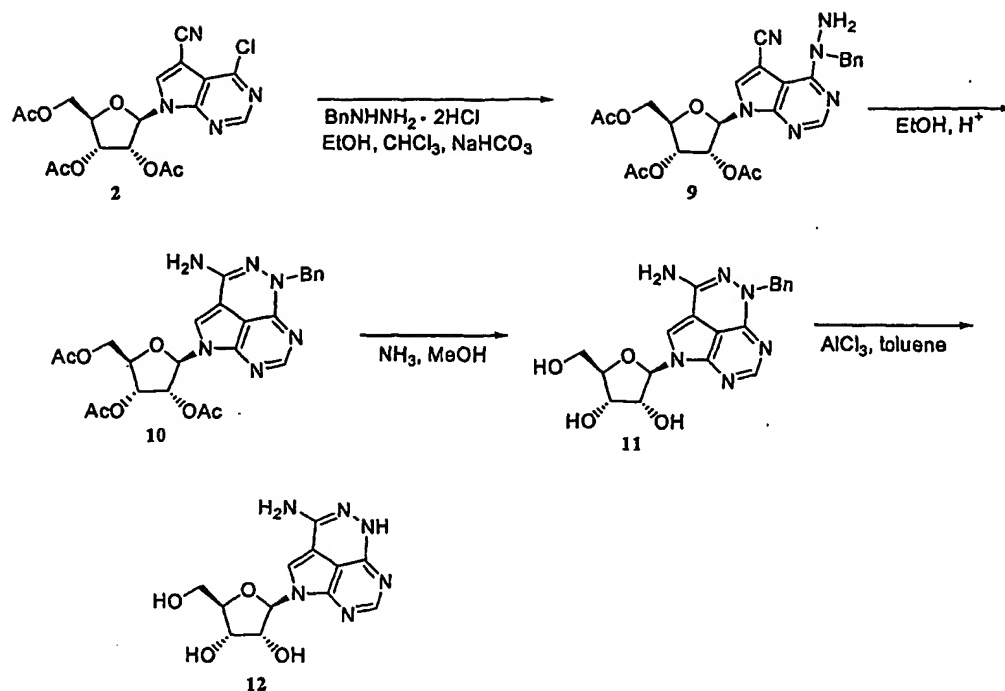


Scheme 12



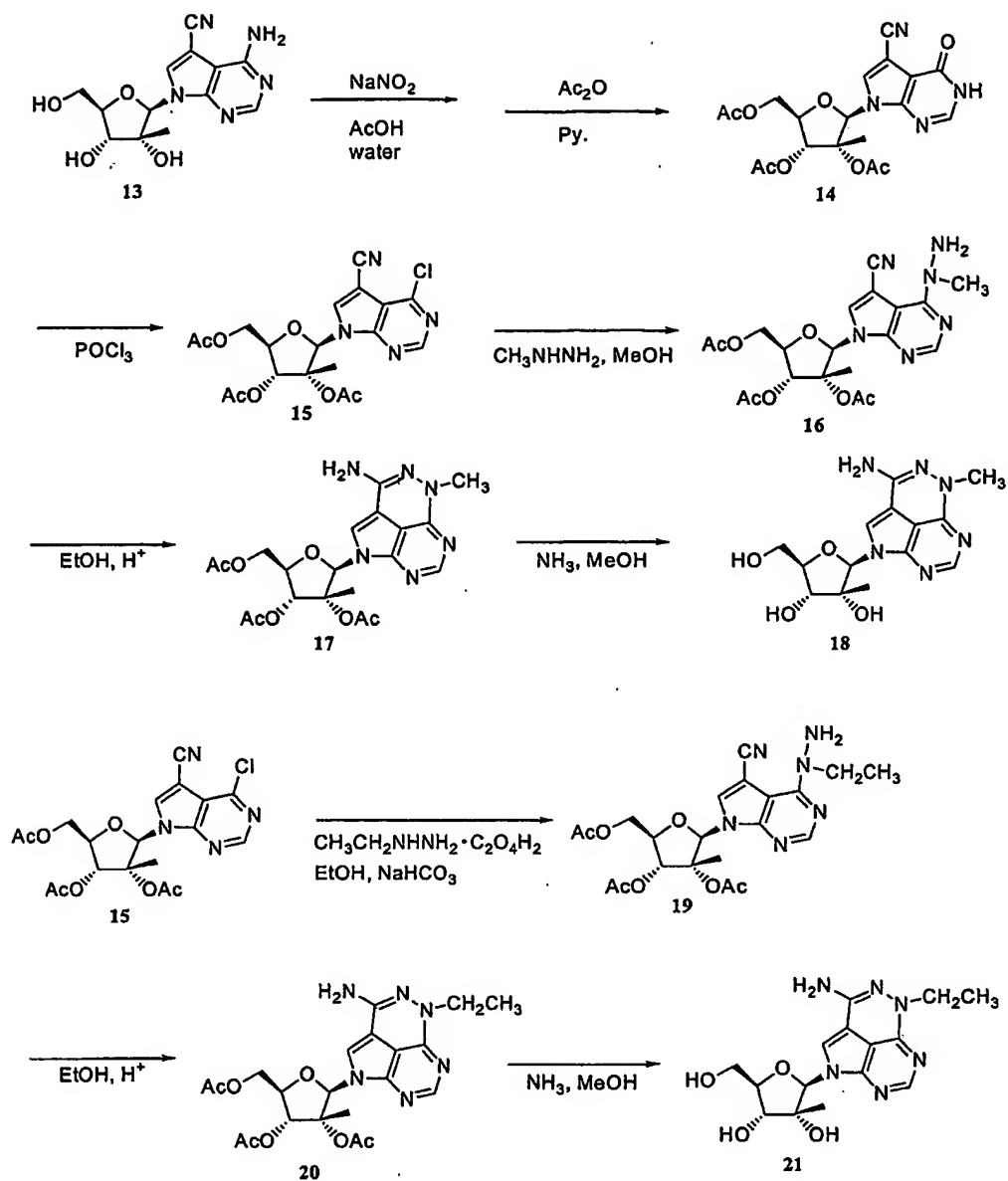
Scheme 13

- 5 Similarly, where hydrogen is a desired substituent (instead of a methyl or ethyl group), benzylhydrazine may be employed as reagent, wherein the benzyl group is subsequently removed from the tricyclic heterocyclic base as depicted in Scheme 14 below.

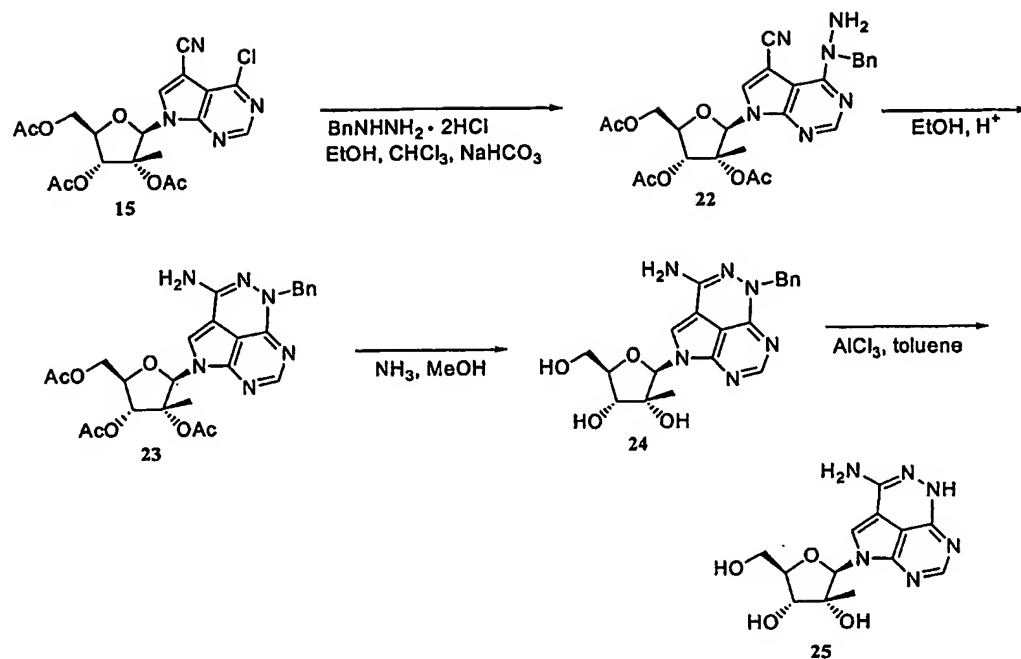


Scheme 14

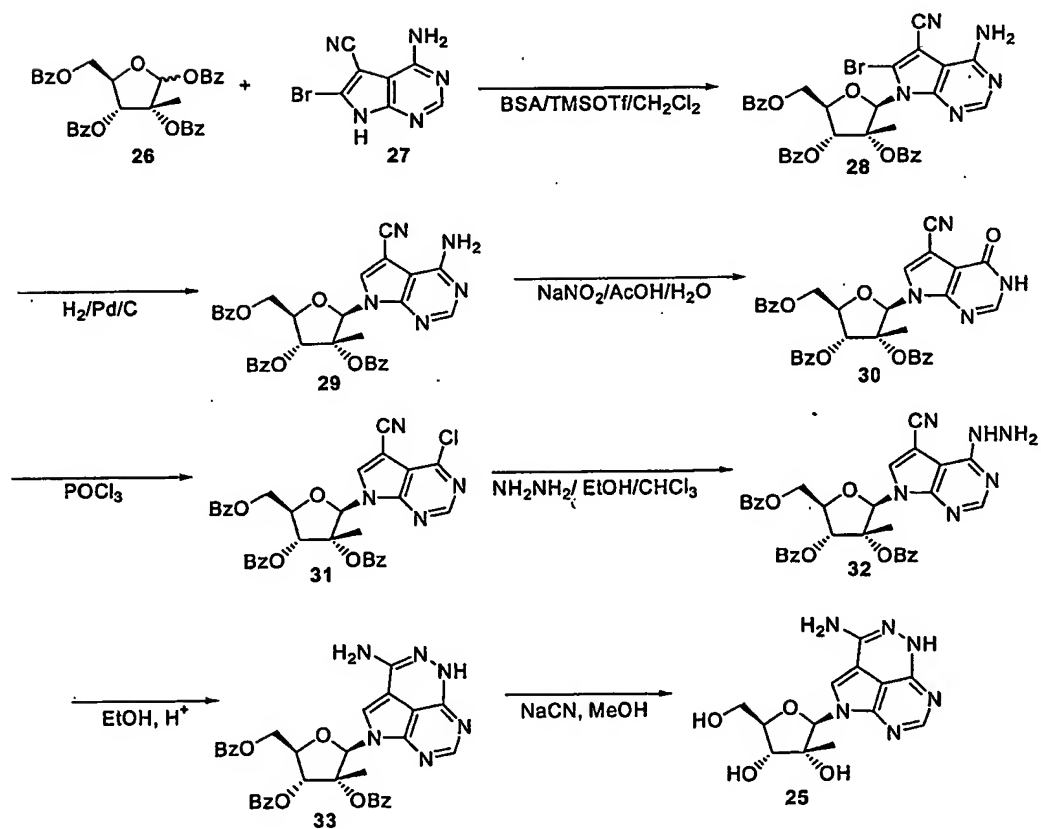
Additionally, or alternatively, where tricyclic nucleosides with a modified sugar portion (*e.g.*,  $\text{C}_2'$ -alkyl) are especially desired, contemplated tricyclic nucleoside libraries may be synthesized as shown in Schemes 15-16 below, in which a 4-chloro-5-cyano-ribofuranosyl-pyrrolo[2,3-d]pyrimidine nucleoside with a 2'-methylribofuranose is reacted in a sequence substantially identical to the reaction sequences of Schemes 12-14 above. Compound 25 was also synthesized by an alternative approach as shown in Scheme 17.



Scheme 15



Scheme 16



## Scheme 17

**Use of Contemplated Libraries and Compounds**

It is generally contemplated that all libraries will comprise one or more nucleosides that have numerous biological activities, and especially contemplated biological activities include *in vitro* and *in vivo* inhibition of DNA and/or RNA polymerases, reverse transcriptases, and ligases. Therefore, contemplated nucleosides will exhibit particular usefulness as *in vitro* and/or *in vivo* antiviral agents, antineoplastic agents, or immunomodulatory agents. Further particularly contemplated uses include those in which the compounds according to the inventive subject matter are employed as antineoplastic agents (e.g., in the treatment of solid or lymphatic tumors).

Particularly contemplated antiviral activities include at least partial reduction of viral titers of respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, Hanta virus (hemorrhagic fever), human papilloma virus (HPV), yellow fever virus, measles virus, as well as viruses in the families of Flaviviridae, Paramyxoviridae, Orthomyxoviridae, Picornaviridae, Bunyaviridae, Arenaviridae, and Herpesviridae. The anti-HCV activity of the nucleosides and libraries were tested by Replicon and BVDV cell-line based assays. The HCV NS5B polymerase activity was tested for the mono-, di-, and triphosphates of the nucleosides or 5'-methylenephosphonate derivatives. The compounds and libraries were tested for their replication of Hepatitis C virus RNA by cell-line based HCV Replicon assay as described in V. Lohmann, F. Korner, J.-O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, "Replication of a Subgenomic Hepatitis C virus RNAs in a Hepatoma Cell Line", *Sciences*, 1999, 285, 110.

Especially contemplated immunomodulatory activity includes at least partial reduction of clinical symptoms and signs in arthritis, psoriasis, inflammatory bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma, but also modulation of some portion of a mammal's immune system, and especially modulation of cytokine profiles of Type 1 and Type 2. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2,

suppression of Type 1 and stimulation of Type 2, or suppression of Type 2 and stimulation of Type 1.

Where contemplated nucleosides are administered in a pharmacological composition, it is contemplated that suitable nucleosides can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated nucleosides can be administered orally as pharmacologically acceptable salts, or intravenously in physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated nucleosides may be modified to render them more soluble in water or other vehicle, which for example, may be easily accomplished by minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient. Thus, it is contemplated that the compounds according to the inventive subject matter may be formulated to provide a pharmaceutical composition comprising such compounds at a concentration effective to provide a desired pharmacological effect (*e.g.*, reduce propagation of a virus in a patient infected with the virus). The terms "reduce propagation of a virus" and "inhibiting propagation of a virus" are used interchangeably herein and refer to a reduction of production of new viruses, wherein the reduction may be due to one or more pharmacological effects. For example, reduction of viral propagation may be achieved by a direct antiviral effect, including competitive, allosteric, non-competitive (or otherwise) inhibition of a viral polymerase (*e.g.*, especially of NS5B of HCV), inhibition of virus entry into a host cell, reduction of proper virus particle assembly, inhibition of viral protein processing. Alternatively, reduction of viral propagation may also be achieved by an indirect antiviral effect, including stimulation of immune response (*e.g.*, enhanced CTL-activation) or modulation of Th1/Th2 balance (*e.g.*, promoting a Th1 response and/or reducing Th2 response).

While it is generally contemplated that administration of such compounds may be systemic or specific to a particular organ, it is typically preferred that the above compounds

may be administered in the form of a prodrug. Particularly suitable prodrug forms of the above compounds may include a moiety that is covalently coupled to at least one of the C2'-OH, C3'-OH, and C5'-OH (or phosphate or modified phosphate group in these positions), wherein the moiety is preferentially cleaved from the compound in a target cell (*e.g.*,  
5 Hepatocyte) or a target organ (*e.g.*, liver). While not limiting to the inventive subject matter, it is preferred that cleavage of the prodrug into the active form of the drug is mediated (at least in part) by a cellular enzyme, particularly receptor, transporter and cytochrome-associated enzyme systems (*e.g.*, CYP-system). Thus, in particularly preferred prodrug forms, the sugar will be covalently coupled to a group that comprises a phosphorus atom (*e.g.*,  
10 phosphate or phosphonate group), wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.

Especially contemplated prodrugs comprise a cyclic phosphate, cyclic phosphonate and/or a cyclic phosphoamidate, which are preferentially cleaved in a hepatocyte to produce the contemplated compounds (as nucleoside or nucleotide). There are numerous such  
15 prodrugs known in the art, and all of those are considered suitable for use herein. However, especially contemplated prodrug forms are disclosed in WO 01/47935 (Novel Bisamidate Phosphonate Prodrugs), WO 01/18013 (Prodrugs For Liver Specific Drug Delivery), WO 00/52015 (Novel Phosphorus-Containing Prodrugs), and WO 99/45016 (Novel Prodrugs For Phosphorus-Containing Compounds), all of which are incorporated by reference herein.  
20 Consequently, especially suitable prodrug forms include those targeting a hepatocyte or the liver.

Still further particularly preferred prodrugs include those described by Renze et al. in Nucleosides Nucleotides Nucleic Acids 2001 Apr-Jul;20(4-7):931-4, by Balzarini et al. in Mol Pharmacol 2000 Nov;58(5):928-35, or in U.S. Pat. No. 6,312,662 to Erion et al., U.S.  
25 Pat. No. 6,271,212 to Chu et al., U.S. Pat. No. 6,207,648 to Chen et al., U.S. Pat. No. 6,166,089 and U.S. Pat. No. 6,077,837 to Kozak, U.S. Pat. No. 5,728,684 to Chen, and U.S. Pat. Appl. Publication No. 20020052345 to Erion, all of which are incorporated by reference herein. Alternative contemplated prodrugs include those comprising a phosphate and/or phosphonate non-cyclic ester, and an exemplary collection of suitable prodrugs is described  
30 in U.S. Pat. No. 6,339,154 to Shepard et al., U.S. Pat. No. 6,352,991 to Zemlicka et al., and U.S. Pat. No. 6,348,587 to Schinazi et al. Still further particularly contemplated prodrug forms are described in FASEB J. 2000 Sep;14(12):1784-92, Pharm. Res. 1999, Aug 16:8



1179-1185, and Antimicrob Agents Chemother 2000, Mar 44:3 477-483, all of which are incorporated by reference herein. In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of various diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

### **Experimental Procedures**

#### *Synthetic Schemes 1-11*

Scheme 1 depicts a general approach for synthesis of contemplated libraries, and it should be appreciated that alternative libraries, and especially the libraries according to Schemes 2-11 may be prepared following substantially identical reaction conditions as described below, and/or reaction conditions well known to a person of ordinary skill in the art (e.g., reaction conditions for Heck, Stille, or Suzuki reactions).

Library 7: To a suspension of sodium hydride (60% in oil, 470 mg) and 7-deazapurine derivative 2 in anhydrous acetonitrile was added ribofuranose chloride 1. The reaction mixture was stirred at room temperature for 5 hours. Aqueous work up and chromatographic purification provided nucleoside 3. This compound was reacted with alkylhydrazine in ethanol and chloroform for 24 hours. Treatment with ammonia methanol solution provided the nucleoside 5. TBDMSCl was used to protect the hydroxyl groups. The 5'-protecting group was selectively removed by TFA and water. The resultant compound was loaded on the MMTCl resin. The resultant resin was reacted with various electrophiles in parallel. Deprotection and cleavage provided the final tricyclic library 7.

*Synthetic Schemes 12-17*

*6-Amino-8-( $\beta$ -D-ribofuranosyl)-4-methylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine*  
(Scheme 12)

4-Chloro-5-cyano-7-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)pyrrolo[2,3-  
5 *d*]pyrimidine (2a). A solution of 5-cyano-4-hydroxy-7-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (1) (0.4 g (0.9 mmol) [B.C. Hinshaw, J. F. Gerster, R. K. Robins and L. B. Townsend, *J. Org. Chem.* 35, 236-241 (1970)] in 30 mL of phosphorous oxychloride was refluxed for 1 h. The reaction mixture was cooled and evaporated. The crude residue was co-evaporated three times with 15 mL portions of chloroform to remove trace  
10 amounts of the acidic solvent. It was then diluted with 15 mL of saturated NaHCO<sub>3</sub>, and the mixture was extracted three times with 20 mL portions of ethyl acetate. The combined organic phase was dried (NaSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by chromatography on a silica gel column (ethyl acetate:hexane = 1:1) to afford 336 mg of the desired compound 2 in 81 % yield.

15 6-Amino-8-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)-4-methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]pyridazine (4). To a stirred solution of methylhydrazine (0.012 mL, 3.2 mmol) in 20 mL of methanol was added 100 mg (2.3 mmol) of compound 2. The mixture was stirred at 25 °C for 5 h under an atmosphere of argon. The reaction mixture was concentrated to afford 3 as a light yellow-colored foam, which was used for next step without  
20 further purification. Thus obtained compound 3 was added to 25 mL of ethanol and a catalytic amount of concentrated HCl. The reaction mixture was heated to reflux for 3 h, then cooled, and concentrated to afford a light yellow-colored foam. The crude product was purified by chromatography on a silica gel column (MeOH:CHCl<sub>3</sub> = 1:9) to afford 42 mg of the desired compound 4 as a tan-colored solid (39 % yield).

25 6-Amino-8-( $\beta$ -D-ribofuranosyl)-4-methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]pyridazine (tricitabine, 5). To 42 mg (0.094 mmol) of intermediate 4 was added 5 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered flask for 16 h. The solvent was evaporated, and the crude product was purified by chromatography on a silica gel column (MeOH:CHCl<sub>3</sub> = 1:9) to afford tricitabine (5) as a  
30 light tan-colored solid in 98% yield (30 mg). <sup>1</sup>H NMR (DMSO):  $\delta$  3.15 (d, 1H, *J* = 5.1Hz), 3.38 (s, 3H), 3.50 (m, 2H), 3.95 (m, 1H), 4.07 (m, 1H), 4.47 (m, 1H), 5.19 (d, 1H, *J* = 4.2Hz),

5.39 (d, 1H,  $J = 9.0$ ), 5.62 (m, 1H), 5.78 (d, 1H,  $J = 6.6\text{Hz}$ ), 6.25 (bs, 1H), 7.05 (s, 1H), 8.00 (s, 1H).

*6-Amino-8-(b-D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine*  
(Scheme 13)

5        **6-Amino-8-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (7).** To 15 mL of anhydrous ethanol was added 42 mg (0.5 mmol) of dry  $\text{NaHCO}_3$ . The mixture was stirred for 20 min, then treated with 18 mg (0.12 mmol) of the oxalate salt of ethylhydrazine. After 30 min, it was treated with 48 mg (0.11 mmol) of compound 2, in 5 mL of  $\text{CHCl}_3$  and stirred for 48 h at 25 °C. Then the solvent was  
10 evaporated and 10 mL of chloroform was added. The insoluble salts were filtered off, and the filtrate was concentrated to afford compound 6 as a light yellow-colored foam, which was used for next step without further purification. Thus obtained compound 6 was added to 15 mL of ethanol and a catalytic amount of concentrated HCl. The resulting mixture was heated to reflux for 8 h, then cooled, and concentrated to afford a light yellow-colored foam. The  
15 crude product was purified by chromatography on a silica gel column ( $\text{MeOH}:\text{CHCl}_3 = 1:9$ ) to afford 37 mg of the desired compound 7 in 72% yield.

**6-Amino-8-( $\beta$ -D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (8).** To 37 mg (0.11 mmol) of intermediate 7 was added 8 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered  
20 flask for 16 h. The solvent was evaporated, and the crude product was purified by chromatography ( $\text{MeOH}:\text{CHCl}_3 = 1:9$ ) on a silica gel column to afford 28 mg of compound 8 as a light tan-colored solid in 76% yield.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OH}$ ):  $\delta$  1.30 (g, 3H,  $J = 6.9\text{Hz}$ ), 3.72 (m, 1H), 3.85 (m, 2H), 4.16 (m, 1H), 4.28 (m, 1H), 5.84 (d, 1H,  $J = 6.9\text{Hz}$ ), 7.07 (s, 1H), 7.99 (s, 1H).

25        *6-Amino-8-(b-D-ribofuranosyl)pyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine*  
(Scheme 14)

**6-Amino-8-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)-4-benzylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (11).** To 7 mL of anhydrous ethanol was added 100 mg (25 mmol) of dry  $\text{NaHCO}_3$ . The mixture was stirred for 20 min, and then treated with 48 mg  
30 (0.25 mmol) of benzylhydrazine dihydrochloride. After 30 min, it was treated with 100 mg

(0.23 mmol) of compound 2 in 1 mL of  $\text{CHCl}_3$  and stirred for 48 h at 25 °C. The solvent was evaporated and 15 ml of chloroform was added. The insoluble salts were filtered off, and the filtrate was concentrated to afford compound 9 as a light yellow-colored foam, which was used for next step without further purification. Compound 9 was added to 15 mL of ethanol and a catalytic amount of concentrated HCl. The resulting mixture was heated to reflux for 16 h, then cooled, and concentrated to afford 10 as a light yellow-colored foam. The crude product was then added to 10 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered flask for 16 h. Then the solvent was evaporated, and the crude product was purified by chromatography on a silica gel column (MeOH: $\text{CHCl}_3$  = 1:9) to afford 36 mg of compound 11 as a light tan-colored solid in 40% yield.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OH}$ ):  $\delta$  3.73 (m, 1H), 3.87 (m, 1H), 4.16 (d, 1H,  $J$  = 2.4Hz), 4.30 (m, 1H), 4.69 (m, 1H), 5.05 (s, 2H), 5.87 (d, 1H,  $J$  = 6.6Hz), 7.10 (s, 1H), 7.27 (m, 5H), 8.03 (s, 1H).

**6-Amino-8-( $\beta$ -D-ribofuranosyl)pyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine (12).**

To 5 mg (0.013 mmol) of benzyl intermediate 11 was added 4 mL of dry toluene, followed by 8.4 mg (0.063 mmol) of  $\text{AlCl}_3$ . The mixture was heated to 65 °C for 1 h, and the cooled reaction mixture was concentrated. The residue was neutralized by the addition of 5 mL of a saturated solution of  $\text{NaHCO}_3$ , and the mixture was stirred for 30 min. The aqueous solvent was removed, followed by the addition of 2 mL of methanol. Then it was filtered through celite, and the filtrate was concentrated. The crude product was purified by reversed phase HPLC to afford 0.2 mg of the desired compound 12 in 5 % yield.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OH}$ ):  $\delta$  3.72 (m, 1H), 3.87 (m, 1H), 4.17 (m, 1H), 4.30 (m, 1H), 4.66 (m, 1H), 5.90 (d, 1H,  $J$  = 3.3Hz), 7.15 (s, 1H), 4.97 (s, 1H).

**6-Amino-8-(2-C-methyl-b-D-ribofuranosyl)-4-methylpyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine (Scheme 15)**

**5-Cyano-7-(2'-C-methyl-2',3',5'-tri-O-acetyl- $\beta$ -D-ribofuranosyl)pyrrolo[2,3-d]pyrimidone (14).** 4-Amino-5-cyano-7-(2'-C-methyl-2',3',5'-tri-O-acetyl- $\beta$ -D-ribofuranosyl)pyrrolo[2,3-d]pyrimidone (13) [Y. Murai, H. Shiroto, T. Ishizaki, T. Iimori, Y. Kodama, Y. Ohtsuka and T. Oishi, *Heterocycles*. 33 (1), 391-404 (1992)]. (155 mg, 0.51 mmol) was dissolved in a mixture of acetic acid and water (10 ml, 1:1). Sodium nitrile (175 mg, 2.5 mmol) was added to the above solution. This mixture was stirred at 70 °C for 1 hour.

TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH=10:1) showed the starting material disappeared. The reaction mixture was concentrated to dryness under vacuum, and the residue was treated with a mixture of acetic anhydride and pyridine (10 ml, 1:1). After stirring for 12 hours at room temperature, the reaction mixture was concentrated to dryness, and the residue was purified on a silica gel column with hexane/ethyl acetate (1:1) to yield 130 mg of the desired product 14 as a white solid in 60% yield; <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.05 (s, 1H), 8.00 (s, 1H), 6.56 (s, 1H), 5.48 (d, 1H, *J* = 6.0 Hz), 4.40 (m, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.38 (s, 3H).

**4-Chloro-5-cyano-7-(2,3,5-tri-*O*-acetyl-2-*C*-methyl-β-*D*-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (15).** To 0.4 g (0.9 mmol) of 5-cyano-4-hydroxy-7-(2,3,5-tri-*O*-acetyl-2-*C*-methyl-β-*D*-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (14) was added 30 mL of phosphorous oxychloride. The mixture was refluxed for 1 h, then cooled, and concentrated. The crude residue was co-evaporated three times with 15 mL portions of chloroform to remove trace amounts of the acidic solvent. It was then diluted with 15 mL of saturated NaHCO<sub>3</sub>, and the mixture was extracted three times with 20 mL portions of ethyl acetate. The combined organic phase was dried (NaSO<sub>4</sub>), and the solvent was evaporated. The residue was purified by chromatography on a silica gel column (ethyl acetate:hexane = 1:1) to afford 336 mg of the desired compound 15 in 81 % yield.

**6-Amino-8-(2,3,5-tri-*O*-acetyl-2-*C*-methyl-β-*D*-ribofuranosyl)-4-methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]pyridazine (17).** To a stirred solution of 0.012 mL (3.2 mmol) of methylhydrazine in 20 mL of methanol was added 100 mg (2.3 mmol) of compound 15. The mixture was stirred for 5 h at 25 °C, under an atmosphere of argon. Then it was evaporated to afford 16 as a light yellow-colored foam, which was used without further purification. Compound 16 was added to 25 mL of ethanol and a catalytic amount of concentrated HCl. It was heated to reflux for 3 h, then cooled, and evaporated to afford a light yellow-colored foam. The crude product was purified by chromatography on a silica gel column (MeOH:CHCl<sub>3</sub> = 1:9) to afford 42 mg of the desired compound 17 as a tan-colored solid (39 % yield).

**6-Amino-8-(2-*C*-methyl-β-*D*-ribofuranosyl)-4-methylpyrrolo-[4,3,2-*de*]pyrimido[4,5-*c*]pyridazine (18).** To 42 mg (0.094 mmol) of intermediate 17 was added 5 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered flask for 16 h. Then the solvent was evaporated, and the crude product was

purified by chromatography on a silica gel column (MeOH:CHCl<sub>3</sub> = 1:9) to afford 2'-C-methyltricyribine (18), as a light tan-colored solid in 98% yield (30 mg). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 7.71 (s, 1H), 6.87 (s, 1H), 3.92 (m, 3H), 3.72 (m, 1H), 3.20 (s, 3H), 0.60 (s, 3H); MS: m/z 335 (M+H)<sup>+</sup>.

5                    *6-Amino-8-(2-C-methyl-β-D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (Scheme 15)*

**6-Amino-8-(2,3,5-tri-O-acetyl-2-C-methyl-β-D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (20).** To 15 mL of anhydrous ethanol was added 42 mg (0.5 mmol) of dry NaHCO<sub>3</sub>. The mixture was stirred for 20 min, and then treated with 18 mg (0.12 mmol) of the oxalate salt of ethylhydrazine. After 30 min, it was treated with 48 mg  
10 (0.11 mmol) of compound 15, in 5 mL of CHCl<sub>3</sub> and stirred for 48 h at 25 °C. Then the solvent was evaporated and 10 mL of chloroform was added. The insoluble salts were filtered off, and the filtrate was concentrated to afford compound 19 as a light yellow-colored foam, which was used without further purification. Compound 19 was added to 15 mL of ethanol  
15 and a catalytic amount of concentrated HCl. The resulting mixture was heated to reflux for 8 h, then cooled, and evaporated to afford a light yellow-colored foam. The crude product was purified by chromatography on a silica gel column (MeOH:CHCl<sub>3</sub> = 1:9) to afford 37 mg of the desired compound 20 as a pale yellow solid in 72% yield.

**6-Amino-8-(2-C-methyl-β-D-ribofuranosyl)-4-ethylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (21).** To 37 mg (0.11 mmol) of intermediate 20 was added 8  
20 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered flask for 16 h. Then the solvent was evaporated and the crude product was purified by chromatography (MeOH:CHCl<sub>3</sub> = 1:9) on a silica gel column to afford 28 mg of compound 21 as a light tan-colored solid in 76% yield.

25                    *6-Amino-8-(2-C-methyl-β-D-ribofuranosyl)-pyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine (Scheme 16)*

**6-Amino-8-(2,3,5-tri-O-acetyl-2-C-methyl-β-D-ribofuranosyl)-4-benzylpyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (24).** To 7 mL of anhydrous ethanol was added 100 mg (25 mmol) of dry NaHCO<sub>3</sub>. The mixture was stirred for 20 min, and then  
30 treated with 48 mg (0.25 mmol) of benzylhydrazine dihydrochloride. After 30 min, it was

treated with 100 mg (0.23 mmol) of compound 15 in 1 mL of  $\text{CHCl}_3$  and stirred for 48 h at 25 °C. Then the solvent was evaporated and 15 ml of chloroform was added. The insoluble salts were filtered off, and the filtrate was concentrated to afford compound 22 as a light yellow-colored foam, which was used without further purification. Compound 22 was added to 15 mL of ethanol and a catalytic amount of concentrated HCl. The resulting mixture was heated to reflux for 16 h, then cooled, and evaporated to afford 23 as a light yellow-colored foam. The crude product was then added to 10 mL of a saturated solution of ammonia in methanol. The resulting mixture was stirred at 25 °C in a stoppered flask for 16 h. Then the solvent was evaporated, and the crude product was purified by chromatography on a silica gel column ( $\text{MeOH}:\text{CHCl}_3 = 1:9$ ) to afford 36 mg of compound 24 as a light tan-colored solid in 40% yield.

**6-Amino-8-(2-C-methyl- $\beta$ -D-ribofuranosyl)-pyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine (25).** To 5 mg (0.013 mmol) of benzyl intermediate 24 was added 4 mL of dry toluene, followed by 8.4 mg (0.063 mmol) of  $\text{AlCl}_3$ . The mixture was heated to 65 °C for 1 h, then cooled, and concentrated. The residue was neutralized by the addition of 5 mL of a saturated solution of  $\text{NaHCO}_3$  and stirring for 30 min. The aqueous solvent was removed, followed by the addition of 2 mL of methanol. Then mixture was filtered through celite, and the filtrate was concentrated. The crude product was purified by reversed phase HPLC to afford 0.2 mg of the desired compound 25 in 5 % yield.

*6-Amino-8-(2-C-methyl- $\beta$ -D-ribofuranosyl)-pyrrolo-[4,3,2-de]pyrimido[4,5-c]pyridazine (Scheme 17)*

1,2,3,5-Tetra-O-benzoyl-2-C-methyl- $\alpha/\beta$ -D-ribofuranose (26) was synthesized based on the literature procedure of Harry-O'kuru, R. E.; Smith, J. M.; Wolfe, M. S. *J. Org. Chem.* 1997, 62, 1754-1759; Wolfe, M. S.; Harry-O'kuru, R. E. *Tetrahedron Lett.* 1995, 36, 7611-7614.

**Compound 28.** To 500 mg (0.86 mmol) of 27 was added 8 mL of dichloroethane. To this was added 0.21 mL (0.86 mL) of BSA and the mixture was stirred for 15 min at 25°C. Then 500 mg (0.86 mmol) of 26 was added in 2 mL of dichloroethane, followed by 0.47 mL (2.6 mmol) of trimethylsilyltrifluoromethanesulfonate in 1.5 mL of dichloroethane. After 15 min, another 0.21 mL (0.86 mL) of BSA was added and the mixture was stirred for 1.5 h at 25°C, followed by 18 h at 62°C. The mixture was then poured over 15 g of cracked ice in the

presence of 1 g of NaHCO<sub>3</sub> and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with three 25 mL portions of ethyl acetate. The combined organic layers were dried (NaSO<sub>4</sub>) and evaporated. Purification by column chromatography afforded the product, as a tan colored solid. Yield 0.27 g (45 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.70 (s, 3H), 4.86 (m, 4H), 5.93 (br s, 2H), 6.87 (s, 1H), 7.02 (d, 1H J = 7.8), 7.30 (m, 3H), 7.48 (m, 4H), 7.61 (m, 2H), 7.95 (d, 2H J = 7.2), 8.13 (d, 3H J = 7.2), 8.37 (s, 1H).

**Compound 29.** To 500 mg of 28 was added 10 mL of dioxane and 2 mL (20 mmol) of triethylamine, followed by a catalytic amount of palladium on carbon. It was shaken under an atmosphere of hydrogen at 30 psi for 2 h then filtered through celite and evaporated to afford 430 mg of 29 (98 %), which was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.61 (s, 1H), 4.71 (m, 2H), 4.94 (m, 2H), 5.78 (br s, 2H), 6.05 (d, 1H J = 5.7), 6.88 (s, 1H), 7.33 (m, 3H), 7.47 (m, 4H), 7.58 (m, 2H), 7.84 (s, 1H), 7.94 (m, 2H), 8.12 (m, 3H), 8.49 (s, 1H).

**Compound 30.** To 100 mg (0.16 mmol) of 29 was added 8.1 mL of a 4:1 mixture of acetic acid and water. The mixture was treated with 113 mg (1.6 mmol) of sodium nitrite and heated in a sealed bomb at 90°C. After 1 h the mixture was diluted with 15 mL of saturated sodium bicarbonate and extracted with three 15 mL portions of dichloromethane. The combined organic phase was dried (NaSO<sub>4</sub>) and evaporated to afford 100 mg of 30 as a yellow foam (99%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.58 (s, 3H), 4.71 (m, 2H), 4.93 (m, 2H), 5.68 (br s, 2H), 6.04 (d, 1H J = 5.7), 6.86 (s, 1H), 7.31 (m, 3H), 7.42 (m, 4H), 7.58 (m, 2H), 7.82 (s, 1H), 7.92 (m, 2H), 8.11 (m, 3H), 8.47 (s, 1H).

**Compound 31.** To 0.3 g (0.48 mmol) of 30 was added 15 mL of phosphorous oxychloride. The mixture was refluxed for 1 h, then cooled and evaporated. The crude residue was co-evaporated three times with 15 mL portions of chloroform to remove trace amounts of the acidic solvent. It was then diluted with 15 mL of saturated NaHCO<sub>3</sub> and extracted three times with 20 mL portions of ethyl acetate. The combined organic phase was dried (NaSO<sub>4</sub>) and evaporated to afford 200 mg of 31 as a tan colored foam (62 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.58 (s, 3H), 4.93 (m, 2H), 5.98 (d, 1H J = 5.4), 6.94 (s, 1H), 7.31 (m, 3H), 7.42 (m, 4H), 7.58 (m, 2H), 7.93 (dd, 2H J = 8.4), 8.10 (m, 3H), 8.14 (s, 1H), 8.83 (s, 1H).

**Compound 33.** To a stirred solution of 2.2 μL (0.07 mmol) of hydrazine in 3 mL of ethanol was added 31 mg (0.05 mmol) of 31. The mixture was stirred for 13 h at 25°C, then



evaporated to afford **32** as a yellow colored foam, which was used immediately without further purification. Then 5 mL of ethanol and a catalytic amount of concentrated HCl was added and the mixture was heated to reflux for 30 min, cooled, and evaporated. The residue was diluted with 10 mL of brine, then extracted with four 10 mL portions of ethyl acetate.

- 5 The combined organic phase was dried (NaSO<sub>4</sub>) and evaporated to afford 19 mg of **33** as a light green colored foam. Yield (61%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.57 (s, 3H), 4.71 (m, 2H), 4.92 (m, 2H), 6.05 (d, 1H J = 5.7), 6.87 (s, 1H), 7.31 (m, 3H), 7.47 (m, 3H), 7.58 (m, 3H), 7.81 (s, 1H), 7.94 (d, 2H J = 7.5), 8.09 (m, 4H), 8.56 (s, 1H); mass spectrum: m/z (M + 1), m/z (M + Na).

- 10 **Compound 25.** To a stirred solution of 19 mg (0.03 mmol) of **33** in 5 mL of methanol was added 8.2 mg (0.17 mmol) sodium cyanide. The resulting mixture was stirred at 25°C for 48 h. Then the solvent was evaporated and the crude product was purified by reversed phase HPLC to afford **25**.

#### *Exemplary Building Blocks for C-C Bond Formation*

- 15 For Heck Reaction: 2-ethynylpyridine, 5-phenyl-1-pentyne, 4-(tert-butyl)phenylacetylene, phenylacetylene, 3-dibutylamino-1-propyne, phenyl propargyl ether, 5-chloro-1-pentyne, 3-diethylamino-1-propyne, 4-phenyl-1-butyne, 1-heptyne, 1-dimethylamino-2-propyne, 1-pentyne, 2-methyl-1-hexene, (triethylsilyl)acetylene, 3-phenyl-1-propyne, methyl propargyl ether, 3-cyclopentyl-1-propyne, 1-ethynylcyclohexene, 3-butyne-20 1-ol, styrene, vinylcyclohexane, 2-(tributylstannyl)furan, 2-(tributylstannyl)thiophene, tetraphenyltin, 3-cyclohexyl-1-propyne, 4-methoxyphenylacetylene, 4-(trifluoromethyl)phenylacetylene, 4-fluorophenylacetylene, 4-pentyn-1-ol, 4-methylphenylacetylene, 1-ethynylcyclopentanol, 3-methyl-1-propyne, 5-cyano-1-pentyne, cyclohexylethyne, 1-ethynylcyclohexene, 5-cyano-1-pentyne, 1-dimethylamino-2-propyne, 25 N-methyl-N-propargylbenzylamine, 2-methyl-1-buten-3-yne, cyclopentylethyne, 4-nitrophenylacetylene, phenyl propargylsulfide, 4-methyl-1-pentyne, propargyl ethylsulfide, 2-prop-2-ynyl-1,5-dihydro-2H-pyrral-2-one, 6-methyl-5-(2-propynyl)-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone and related end-alkenes and alkynes.

- 30 For Stille Reaction: tetraethyltin, 2-(tributylstannyl)pyridine, tributylstannyl-4-tert-butylbenzene, ethynyltri-n-butyltin, vinyltri-n-butyltin, allyltri-n-butyltin, phenylethynyltri-n-

butyltin, phenyltri-n-butyltin, (2-methoxy-2-cyclohexen-1-yl)tributyltin, 5,6-dihydro-2-(tributylstannyl)-4H-pyran, tri-n-butyl(2-furanyl)tin, tri-n-butyl(2-thienyl)tin, tributyl(phenylethenyl)tin, 4-fluoro-(tri-n-butylstannyl)benzene, 5-fluoro-2-methoxy(tri-n-butylstannyl)benzene, 1-methyl-2-(tributylstannyl)-1H-pyrrole, 5-methyl-2-  
5 tributylstannylthiophene, 2-tributylstannylthiazole, 2-tributylstannylpyrazine, tributyl[3-(trifluoromethyl)phenyl]stannane and other related organic tin reagents.

For Suzuki Reaction: phenylboronic acid, 4-tolylboronic acid, 2-thiopheneboronic acid, thiophene-3-boronic acid, furan-2-boronic acid, cyclopentylboronic acid, 4-methylfuran-2-boronic acid, 3-hydroxyphenylboronic acid, 5-methylfuran-2-boronic acid,  
10 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, (5-formyl-3-furanyl)boronic acid, furan-3-boronic acid and other related organic boronic acids.

Furthermore, all known (and preferably commercially available) aliphatic, aromatic and heterocyclic acyl chlorides, sulfonyl chlorides, isocyanates, thioisocyanates, carboxylic acids, amino acids, isocyanides, halogenated heterocycles and other electrophiles may be  
15 used for the library synthesis.

### **Biological Assays**

The following assays were used to measure the inhibition of HCV, influenza, BVDV, HIV, RSV, HRV, HBV, and cytotoxicity as described below. The inventors have discovered that selected compounds, and particularly selected 2'-beta-methyl nucleoside analogs show  
20 good quality antiviral activities.

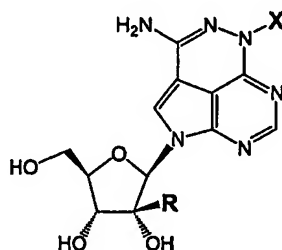
#### *HCV Replicon Assay*

The replicon cells (Huh-7) contain replicating HCV replicon RNA, which was modified in the structural region (replacing the structural region with a neomycin resistance marker). Survival of the replicon cells under G418 selection relies on the replication of HCV  
25 RNA and subsequently expression of neomycin phosphoryltransferase. The ability of modified nucleoside libraries and compounds to suppress HCV RNA replication was determined using the Quantigene Assay Kit from Bayer. The assay measures the reduction of HCV RNA molecules in the treated cells. Replicon cells were incubated at 37°C for 3 days in the presence of nucleoside libraries and compounds before being harvested for detection. The  
30 HCV subgenomic replicon cell line was provided by Dr. Bartenschlager. The assay protocol

was modified based on literature procedure (V. Lohmann, F. Korner, J. O. Koch, U. Herian, L. Theilmann, R. Bartenschlager, *Science*, 1999, 285, 110-113).

*Activity of Selected Contemplated Compounds*

Biological activity of the compounds in the HCV replicon assay is indicated in Table 1 below, wherein A refers to an  $EC_{50} < 10 \mu M$ , B refers to an  $EC_{50} = 10-100 \mu M$ , and C refers to an  $EC_{50} > 100 \mu M$ .



Compound No.	2'-R	X	HCV Replicon, $EC_{50}$
5	H	$CH_3$	A
6	H	$CH_2CH_3$	A
11	H	$CH_2Ph$	C
12	H	H	A
18	Me	$CH_3$	A
21	Me	$CH_2CH_3$	A
24	Me	$CH_2Ph$	C
25	Me	H	A

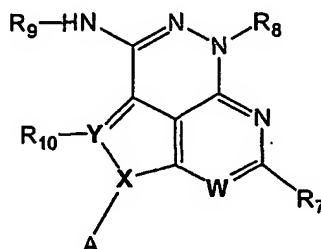
Consequently, the inventors contemplate a method of inhibiting propagation of a virus, wherein the virus is presented with a compound according to the inventive subject matter at a concentration effective to reduce the propagation of the virus. Particularly contemplated viruses include the HCV virus, and it should be recognized that the propagation may be *in vitro* in hepatocytes as well as *in vivo* in a patient infected with the virus. Of course it should be recognized that the compound may be administered directly or that the compound may be converted in the hepatocyte from a prodrug (in a nucleoside or nucleotide form).

Thus, specific embodiments and applications of contemplated compounds and methods for preparing same have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms “comprises” and “comprising” should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

## CLAIMS

What is claimed is:

1. A compound having a structure according to Formula 1:



5

Formula 1

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH;

- 10 R<sub>8</sub> is H, hydroxyalkyl, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkenyl, C<sub>1</sub>-C<sub>8</sub>-alkynyl, C<sub>3</sub>-C<sub>15</sub>-aryl, alkaryl, or C<sub>3</sub>-C<sub>15</sub>-heterocycle;

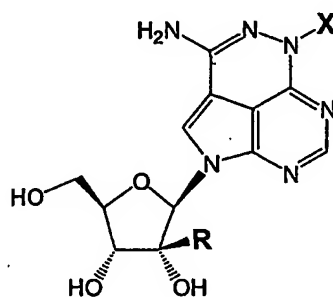
R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

- 15 R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; and

R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring.

- 20 2. The compound of claim 1 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.

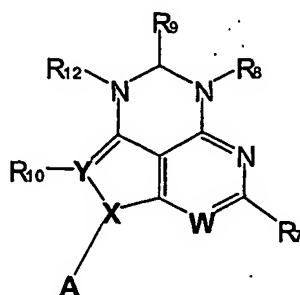
3. The compound of claim 2 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.
4. The compound of claim 1 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.
5. The compound of claim 4 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.
6. The compound of claim 5 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.
7. The compound of claim 1 having a structure according to Formula 1A:



Formula 1A

wherein R is hydrogen or lower alkyl, and wherein X is hydrogen, alkyl, or alkaryl.

8. The compound of claim 7 wherein R is methyl, and wherein X is methyl, ethyl, hydroxyalkyl, or CH<sub>2</sub>-phenyl.
9. A compound having a structure according to Formula 2:



*Formula 2*

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH;

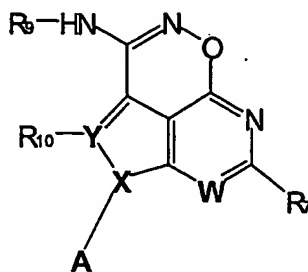
R<sub>8</sub>, R<sub>9</sub>, and R<sub>12</sub> are independently H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; and

R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring.

10. The compound of claim 9 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.
11. The compound of claim 10 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.
12. The compound of claim 9 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.
13. The compound of claim 12 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.
14. The compound of claim 13 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.

15. A compound having a structure according to Formula 3:



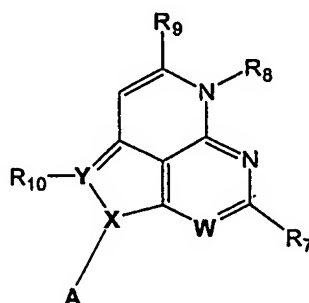
Formula 3

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

- 5  $R_7$  is H,  $NH_2$ ,  $NHR$ ,  $NHCOR$ ,  $NRR'$ ,  $NHSO_2R$ ,  $NHCONHR$ ,  $NHCSNHR$ ,  $CH_2NHR$ ,  $CHRNHR'$ ,  $NHNH_2$ , CN, alkyl, amino alkyl, alkenyl, alkynyl,  $CH_2$ -aryl,  $CH_2$ -heterocycle, halogen, OH, OR, SR, or SH;
- $R_9$  is H, OH, SH, CN, SR, OR,  $SNH_2$ ,  $SNHR$ ,  $C(=NH)NH_2$ ,  $C(=NH)RR'$ ,  $C(=NH)NHOH$ ,  $C(=NH)NHOR$ ,  $C(=NH)NHNH_2$ ,  $C(=NH)NHNRR'$ ,  $NHCOR$ , OR, CSR, SOR,  $SO_2R$ , CONHR, CSNHR, or R;
- 10  $R_{10}$  is H, OH,  $NH_2$ ,  $NHR$ ,  $NHCOR$ ,  $NHNH_2$ ,  $NHNHR$ , alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR,  $CONH_2$ , CONHR, CONRR', or may be null where Y is N; and
- R and R' are independently hydrogen,  $CH_3$ ,  $C_2$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl,  $C_5$ - $C_{12}$  heterocycle or  $C_5$ - $C_{12}$  aromatic ring.
- 15
16. The compound of claim 15 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.
17. The compound of claim 16 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.
- 20 18. The compound of claim 15 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.



19. The compound of claim 18 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.
20. The compound of claim 19 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.
21. A compound having a structure according to Formula 4:



Formula 4

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

- 10  $R_7$  is H,  $NH_2$ , NHR, NHCOR,  $NRR'$ ,  $NHSO_2R$ ,  $NHCONHR$ ,  $NHCSNHR$ ,  $CH_2NHR$ ,  $CHRNHR'$ ,  $NHNH_2$ , CN, alkyl, amino alkyl, alkenyl, alkynyl,  $CH_2$ -aryl,  $CH_2$ -heterocycle, halogen, OH, OR, SR, or SH;

$R_8$  and  $R_9$  are independently H, OH, SH, CN, SR, OR,  $SNH_2$ , SNHR,  $C(=NH)NH_2$ ,  $C(=NH)RR'$ ,  $C(=NH)NHOH$ ,  $C(=NH)NHOR$ ,  $C(=NH)NHNH_2$ ,  $C(=NH)NHNRR'$ , NHCOR, OR, CSR, SOR,  $SO_2R$ , CONHR, CSNHR, or R;

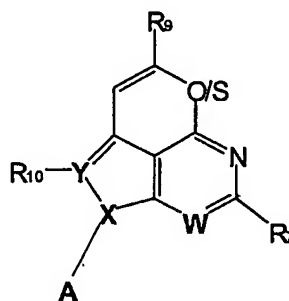
15

$R_{10}$  is H, OH,  $NH_2$ , NHR, NHCOR,  $NHNH_2$ ,  $NHNHR$ , alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR,  $CONH_2$ , CONHR, CONRR', or may be null where Y is N; and

- R and R' are independently hydrogen,  $CH_3$ ,  $C_2$ - $C_8$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl,  $C_5$ - $C_{12}$  heterocycle or  $C_5$ - $C_{12}$  aromatic ring.
- 20

22. The compound of claim 21 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.

23. The compound of claim 22 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.
24. The compound of claim 21 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.
- 5 25. The compound of claim 24 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.
26. The compound of claim 25 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.
- 10 27. A compound having a structure according to Formula 5:



Formula 5

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

- 15 R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH;

R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

- 20 R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; and

R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring.

28. The compound of claim 27 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.

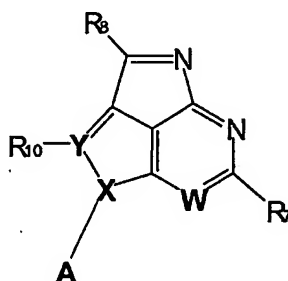
5 29. The compound of claim 28 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.

30. The compound of claim 27 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.

10 31. The compound of claim 30 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.

32. The compound of claim 31 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.

33. A compound having a structure according to Formula 6:



Formula 6

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

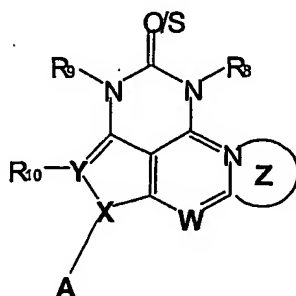
R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH;

$R_9$  is H, OH, SH, CN, SR, OR,  $SNH_2$ ,  $SNHR$ ,  $C(=NH)NH_2$ ,  $C(=NH)RR'$ ,  
 $C(=NH)NHOH$ ,  $C(=NH)NHOR$ ,  $C(=NH)NHNH_2$ ,  $C(=NH)NHNRR'$ ,  
 $NHCOR$ , OR, CSR, SOR,  $SO_2R$ , CONHR, CSNHR, or R;

- 5  $R_{10}$  is H, OH,  $NH_2$ ,  $NHR$ ,  $NHCOR$ ,  $NHNH_2$ ,  $NHNHR$ , alkyl, alkenyl, alkynyl, aryl,  
 alkyaryl, heterocycle, aryl, halogen, COOR,  $CONH_2$ , CONHR, CONRR', or  
 may be null where Y is N; and

R and R' are independently hydrogen,  $CH_3$ ,  $C_2-C_8$  alkyl,  $C_2-C_8$  alkenyl,  $C_2-C_8$  alkynyl,  
 $C_5-C_{12}$  heterocycle or  $C_5-C_{12}$  aromatic ring.

34. The compound of claim 33 wherein the sugar comprises a ribofuranose, a C2'-  
 10 substituted ribofuranose, or a C3'-substituted ribofuranose.
35. The compound of claim 34 wherein the C2'-substituted ribofuranose is C2'-beta-  
 methylribofuranose.
36. The compound of claim 33 wherein the sugar is covalently coupled to a group that  
 comprises a phosphorus atom.
- 15 37. The compound of claim 36 wherein the group comprises a phosphate or phosphonate  
 group, and wherein the phosphate or phosphonate group is further covalently coupled  
 to a removable group that is selectively removed in a liver cell.
38. The compound of claim 37 wherein the removable group forms a cyclic diester with  
 the phosphate or phosphonate group.
- 20 39. A compound having a structure according to Formula 7:




Formula 7

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

R<sub>8</sub> and R<sub>9</sub> are independently H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>,  
C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>,  
C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

5 R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR',  
C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR',  
NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl,  
alkyaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or  
10 may be null where Y is N;

wherein  is an aromatic ring or a heterocyclic ring; and

R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl,  
C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring.

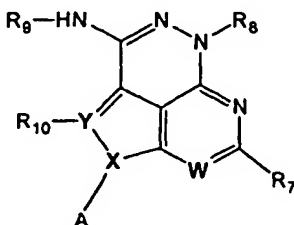
40. The compound of claim 39 wherein the sugar comprises a ribofuranose, a C2'-  
15 substituted ribofuranose, or a C3'-substituted ribofuranose.
41. The compound of claim 40 wherein the C2'-substituted ribofuranose is C2'-beta-methylribofuranose.
42. The compound of claim 39 wherein the sugar is covalently coupled to a group that comprises a phosphorus atom.
- 20 43. The compound of claim 42 wherein the group comprises a phosphate or phosphonate group, and wherein the phosphate or phosphonate group is further covalently coupled to a removable group that is selectively removed in a liver cell.
44. The compound of claim 43 wherein the removable group forms a cyclic diester with the phosphate or phosphonate group.
- 25 45. A pharmaceutical composition comprising a compound according to any one of claim 1, claim 7, claim 9, claim 15, claim 21, claim 27, claim 33, or claim 39 at a

- concentration effective to reduce propagation of a virus in a patient infected with a virus.
46. The pharmaceutical composition according to claim 45 wherein the virus is an HCV virus.
- 5 47. A method of inhibiting propagation of a virus, comprising presenting the virus with a compound according to any one of claim 1, claim 7, claim 9, claim 15, claim 21, claim 27, claim 33, or claim 39 at a concentration effective to reduce the propagation of the virus.
48. The method of claim 47 wherein the virus is an HCV virus.
- 10 49. The method of claim 48 wherein the virus propagates in a hepatocyte.
50. The method of claim 49 wherein the compound is converted in the hepatocyte from a prodrug.

## AMENDED CLAIMS

[received by the International Bureau on 09 June 2003 (09.06.03)  
claim 1 amended]

1. A compound having a structure according to Formula 1:



Formula 1

wherein A is a sugar, and X, Y, W are independently N, C, CH, CR, S, or P;

R<sub>7</sub> is H, NH<sub>2</sub>, NHR, NHCOR, NRR', NHSO<sub>2</sub>R, NHCONHR, NHCSNHR, CH<sub>2</sub>NHR, CHRNHR', NHNH<sub>2</sub>, CN, alkyl, amino alkyl, alkenyl, alkynyl, CH<sub>2</sub>-aryl, CH<sub>2</sub>-heterocycle, halogen, OH, OR, SR, or SH;

R<sub>8</sub> is H, hydroxyalkyl, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkenyl, C<sub>1</sub>-C<sub>8</sub>-alkynyl, C<sub>3</sub>-C<sub>15</sub>-aryl, alkaryl, or C<sub>3</sub>-C<sub>15</sub>-heterocycle;

R<sub>9</sub> is H, OH, SH, CN, SR, OR, SNH<sub>2</sub>, SNHR, C(=NH)NH<sub>2</sub>, C(=NH)RR', C(=NH)NHOH, C(=NH)NHOR, C(=NH)NHNH<sub>2</sub>, C(=NH)NHNRR', NHCOR, OR, CSR, SOR, SO<sub>2</sub>R, CONHR, CSNHR, or R;

R<sub>10</sub> is H, OH, NH<sub>2</sub>, NHR, NHCOR, NHNH<sub>2</sub>, NHNHR, alkyl, alkenyl, alkynyl, aryl, alkaryl, heterocycle, aryl, halogen, COOR, CONH<sub>2</sub>, CONHR, CONRR', or may be null where Y is N; and

R and R' are independently hydrogen, CH<sub>3</sub>, C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, C<sub>5</sub>-C<sub>12</sub> heterocycle or C<sub>5</sub>-C<sub>12</sub> aromatic ring; and

with the proviso that where A is beta-D-ribofuranosyl, X is N, Y is C, R<sub>10</sub> is H, R<sub>7</sub> and R<sub>9</sub> are H, then R<sub>8</sub> is not C<sub>1</sub>-C<sub>8</sub>-alkyl.

2. The compound of claim 1 wherein the sugar comprises a ribofuranose, a C2'-substituted ribofuranose, or a C3'-substituted ribofuranose.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/31369

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(7) : A01N 43/04; A61K 31/70 US CL : 514/43 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/43; 536/18.7, 22.1, 26.1, 27.1, 28.1, 28.6, 55 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) USPATFULL, REGISTRY, CAPLUS, MEDLINE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,633,235 A (TOWNSEND et al.) 27 May 1997 (27.05.1997), columns 1-2.	1-8 and 40-45
Y	US 5,827,833 A (TOWNSEND et al.) 27 October 1998 (27.10.1998), column 2, lines 16-56.	1-8 and 40-45
Y	US 4,123,524 A (TOWNSEND et al.) 31 October 1978 (31.10.1978), columns 1-3.	1-8 and 40-45
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 10 March 2003 (10.03.2003)		Date of mailing of the international search report <b>08 APR 2003</b>
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Patrick T. Lewis Telephone No. 703-308-0196



# INTERNATIONAL SEARCH REPORT

PCT/US02/31369

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

- I. Claims 1-8 and 45-50, drawn to compounds of Formula 1 and compositions.
- II. Claims 9-14 and 45-50, drawn to compounds of Formula 2 and compositions.
- III. Claims 15-20 and 45-50, drawn to compounds of Formula 3 and compositions.
- IV. Claims 21-26 and 45-50, drawn to compounds of Formula 4 and compositions.
- V. Claims 27-32 and 45-50 drawn to compounds of Formula 5 and compositions.
- VI. Claims 33-38 and 45-50, drawn to compounds of Formula 6 and compositions.
- VII. Claims 39-50, drawn to compounds of Formula 7 and compositions.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: PCT Rule 13.2 requires that unity of invention exists only when there is a shared same or corresponding technical feature among the claimed inventions. All the groupings are directed to tricyclic nucleosides but each group has a different special technical feature not shared by the remaining groups. Group I is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 1. Group II is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 2. Group III is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 3. Group IV is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 4. Group V is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 5. Group VI is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 6. Group VII is directed to tricyclic nucleosides and compositions which has a special technical feature of a structural core represented by Formula 7. Each Group has a different special technical feature based upon different structural chemical core. The variability in the heteroatoms included in the various core structures and variability in substituents attached to the different cores supports the examiner's position that the multiple inventions do indeed lack a special technical feature which unifies the various compounds claimed.